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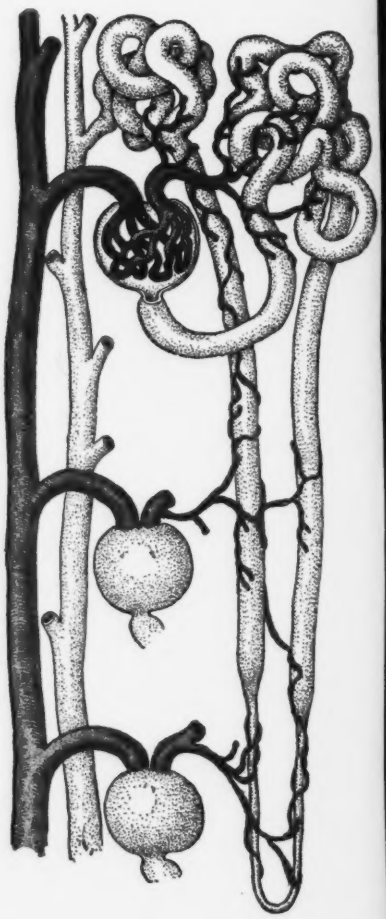

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Circulation

MAY 1955
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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Charles Laubry Lecture

Leadership in Cardiology

By SIR JOHN PARKINSON, M.D. (LOND.), HON. LL.D. (GLAS.), HON. D.SC. (N.U.I.), F.R.C.P., HON. F.R.C.P.E., HON. F.A.C.P.

IT IS at the invitation of the International Council of Cardiology and its President, Dr. Paul White, that I deliver this lecture which is given in honor of Professor Charles Laubry, the first president of the first International Congress of Cardiology held in Paris in 1950, whom we are so pleased to see here today as Honorary President. For the British Cardiac Society and for me, this is a great distinction and I want to express my warm thanks to the Council for it. As I have nothing new to offer you, our President has allowed me to voice what is in my mind and memory. In my mind is the realization that the progress of cardiology has been mainly due to a succession of individuals who proved to be leaders in thought, in action, and notably in discovery. In my memory is the state of Medicine, including cardiology, when I began as a young student 50 years ago, and the transformation that has since taken place. I propose to speak on three separate subjects: first, of those early days and of that great leader James Mackenzie; second, on specialism and the training of the cardiologist; and third, on French cardiology and the leadership of Professor Laubry.

May I look back at Medicine as I found it in my own circle at the London Hospital? The study of the basic sciences was limited to two years of inorganic chemistry, physics, and biology. Then followed two years of anatomy, happily under Sir Arthur Keith, while physiology was too largely a system of conflicting hypotheses though not for my own teacher, Leonard Hill. All this being over, it was then our lot to live for as many hours as possible with the sick in the wards and out-patient clinics, learning by precept and practice what was wrong with them and what to do for them. We learned only what our teachers knew except for what was in our text-books, the most popular of which was Osler's. We had no research consciousness though we were forced to be clinically conscious. In medicine our dozen teachers were equally chiefs, but looking back, how unalike in their attitudes and talents! Outstanding was Henry Head, an inspiring teacher, but admittedly odd in having research on the brain and even submitting to experimental operations on his own nerves. Otherwise research had no place in the wards; it was none of our business. We were busy learning from our elders; and there was a wide variety of approach, a wealth of practical experience in those who moulded us. One teacher, one professor, is never enough; the more the better —and often the merrier. Among them was that fountain of clinical wisdom, Sir Robert Hutchison who is still with us and who prayed that we might be delivered "From inability to let well alone; from too much zeal for the new, and contempt for what is old; from putting knowledge before wisdom, science before art,

The Charles Laubry Lecture was delivered at the II International Congress of Cardiology at Washington, D. C., on Sept. 17, 1954.

cleverness before common sense; from treating patients as cases; and from making the cure more grievous than the ill."

During my medical apprenticeship our clinical practice was mostly empirical and we were not bothered by technics. As a clinical clerk I did use the first sphygmomanometer in the hospital, and a thin X-ray film would drift into the ward, though it might show little beyond the fingermarks of the radiographer. There was then no separate science of psychology, but patients were nursed and treated as kindly as today though with less understanding, for the state of mind of the sick was not studied. Sex did not exist as a subject to be taken into account by all doctors. I had read Oliver Wendell Holmes, however, and he said "The sound of a kiss is not so loud as that of a cannon, but its echo lasts a great deal longer." There were two kinds of heart disease, valvular and nonvalvular, and we were satisfied. Digitalis was given for heart failure in the wards, but forbidden to out-patients. Antibiotics were scarcely on the horizon, and infections ran their course. Many physicians had lost faith in therapeutics and patients were pacified with traditional remedies culled from the hospital pharmacopoeia.

In these last 50 years, medical practice has become more rational, while advance by experiment has largely replaced advance by observation, yet there is still ample scope in clinical science for patient observation. I have been impressed by the way that the science of mind, psychology, has gradually permeated practical medicine. Doctors more often, and more exactly, try to realize in their own minds the position and feelings of their patients. This studied humanism has largely taken the place of what was called the art of medicine. Indeed today we may speak more simply and truly of the Science of Medicine. It has been said that he is the best physician who inspires hope, but too often he brought "no other medicine but only hope," no material benefit. Comparing the past with the present, it is surely in *treatment* that advances of the greatest magnitude have been made. The medical profession is greatly strengthened by the goodwill and moral support of the community, and nothing has elevated medicine in public esteem more than the spectacular progress in medical and surgical treatment in recent years.

How then has medicine, and with it cardiology, grown? It is surely a story of men. It is biography. It is the life and achievement of a succession of men and women—a few of them geniuses, many talented, and a host with fewer gifts but determined to use them well. Thus in a volume like Herrick's *Short History of Cardiology* we read a story of persons and their ideas and achievements rather than a summary of theoretical and factual progress.

In our boyhood and youth we all had our heroes, bright and shining, maybe historical or fictitious or martial, but scarely political and not at that time medical. As we emerged from boyhood and came to the study of Medicine this hero-worship was still strong in us, persisting through our medical training; and many of our teachers became and remain our heroes. You will agree that this faculty of admiration, hero-worship, can and often does persist, and that it still exerts a power in our lives. It has truly been said that we are a part of all that we have met.

People vary a great deal in the way they allow others to influence them. Many are self-sufficient, sure of themselves, independent. Incidentally, it has always been a surprise to me that Americans, whom the world regards as particularly independent and unsubmissive to authority, should be so devoted to their heroes, national, social, and medical. Despite their inveterate fondness for something new and their urge to pursue the impossible, they are catholic in their search for truth and love of learning. Nowhere have the famous physicians of the past, and of every country, been held in greater honor than in the United States.

May I now remind you of the life and work of Sir James Mackenzie, the centenary of whose birth occurred last year. At the age of 25, he joined a busy general practice in Burnley, a Lancashire industrial town where, for 28 years, he practised medicine, midwifery, and some surgery. It was under these conditions, seemingly so unfavorable for such work, that the greater part of his original observations and researches was made. Up to this time neither

he himself nor others had much confidence in his powers or promise; his was a brain that developed slowly. The stimulus proved to be the shock of realizing his ignorance, his inability to understand or deal with the painful problems that faced him daily. One such was the unexpected death in childbirth of a woman under his care from heart failure. He could not understand how or why it had happened or how it could have been recognized in time. Such events stirred him to discontent and so he consulted books and journals but found no satisfaction. He did not know. It did not seem to be known. He would find out. We cannot doubt that deep feeling has often been the spring of medical research. It may thus depend on a man's upbringing and character, and his devotion to an ideal. So Mackenzie set to work to study common symptoms like fatigue, dyspnea, and pain, and to learn their significance by noting their clinical course over the years. Impatient only with his lack of knowledge, he patiently took notes and made records year after year with a sphygmograph and later with the polygraph he devised but in which he took little pride. Here was a genius for taking pains but a common sense that kept technic in its place as a servant and not a master.

It had always been assumed that pain and tenderness arose directly from an organ, but Mackenzie gave the first description of hyperesthetic skin areas associated with disease of particular viscera. He showed that pain and tenderness were referred from an organ to the spinal sensory centers and thence projected to the periphery. Such a "viscerosensory reflex" explained the curious extensions of pain in angina pectoris. At the same time and independently, Henry Head was elaborating similar views which were published a few months after Mackenzie's.

Herrick, whose death this year we lament, wrote "It was largely through Mackenzie's influence that the term 'heart failure' lost much of the opprobrium that had attached to it." Indeed it was not regarded as a proper subject for clinical investigation until Mackenzie convinced the world that the subject of heart failure was of paramount importance in heart disease, and its prevention and treatment the ultimate goal. A similar revival of hope resulted from his teaching, based upon long observations on sinus arrhythmia, extrasystoles, and on murmurs which were compatible with good health. In a clinical sense he isolated auricular fibrillation, at least in its relation to failure and to its particular response to digitalis.

In 1902 appeared that remarkable book *The Study of the Pulse* which had no wide circulation but was quickly seized by the discerning as proof that a great investigator had been quietly at work for 20 years. In 1908 came his *Diseases of the Heart* and in 1909 *Symptoms and their Interpretation* which together showed Mackenzie to be the most original and vigorous mind engaged in this sphere; and people began to talk of the "new" cardiology. What was new was the critical, the scientific approach, and the introduction of hope into what had seemed so largely hopeless.

In 1907 he had left general practice for consulting and hospital work in London. In a few years he became Physician to the Cardiac Department of the London Hospital, where he continued his researches and influenced the many physicians who came to his wards. As years went by, he was limited physically by angina pectoris and in 1925 he died in London from cardiac infarction.

What kind of man was Mackenzie to meet? He was Scottish in appearance and in accent, a massive figure with a slight stoop. His bearded face, with its large brow, was carried by a large and noble head. His eyes were searching, twinkling and friendly as his face was lit by a gentle smile, though not too often. In general he was serious-minded and looked it, but there was a simple blunt humor near the surface. Socially he was warmhearted without being genial. He was gentle in his dealings with patients, especially women, more exigent towards his assistants, yet appreciative. Thus he was mightily pleased with his first resident, soon to be lost in the first world war, who took better polygrams than he could himself.

Though not by nature of a pugnacious temperament, he was a fighter for his opinions, and he had to be. There was little appreciation and some opposition from many of the older physicians of his day. I was warned of the risks

I took by becoming his chief assistant. What a universal change there has been in the common attitude towards what is new, when it is true, and for this I believe we have largely to thank the Americans!

Mackenzie, you will have gathered, found it hard to be satisfied, yet it was a calm and hard-headed man who carried that unquiet and inquiring mind. More, he was a happy man, secretly gratified by his achievements and their recognition, proud to have such friends as Cushny, Keith, Allbutt, Osler, Wenckebach and Thomas Lewis, and constantly sustained by the deep and abiding affection which existed between him and his wife.

The second of my three subjects is *Specialism and the Training of the Cardiologist*. Specialism has been called the growing point of knowledge, and it is to specialism, disintegration in a sense, that the splendid advances of the last half-century have been mainly due. Though many have opposed it, notice that no one has encouraged specialism; indeed that would be superfluous in so natural a process. I remember well the time when medicine was held to be indivisible, and cardiology was not regarded as an integral branch of it. The word cardiologist was not in use, or it was used unkindly, while today a cardiologist claims to be as truly a physician as any other. The stock criticism was that specialism engenders a narrowness of view, bad for the doctor himself and for his patients. But, as Hughlings Jackson said, "There is no harm in studying a special subject; the harm is in doing any kind of work with a narrow aim and a narrow mind." In cardiology, as in other branches, a new and broader outlook has developed; it becomes more and more general. The true specialist looks anywhere and everywhere for the means of cure and prevention. All the physical, mental, and social factors relevant to his own subject are considered and integrated by him as they never were before.

In some quarters there are still attempts to force trained and mature men to abide by the past custom of claiming acquaintance with the whole of general medicine. But many young physicians are attracted by the wide scope and variety of service which a special study of the circulation and its diseases offers. Medicine has divided. It already has children—the present specialties; and now the grandchildren, the subdivisions—perhaps to be future specialties—are growing up around us. Normal parents take pride in their offspring and are particularly tolerant towards their grandchildren. The subdivision or differentiation which has come to pass in medicine as a whole is now affecting us in cardiology. An instance is vascular disease, and the multifarious program of this congress proves the fact, for it is full of diverse subjects or subspecialties.

As a cardiologist, my personal attitude towards further specialization can be simply stated. Each individual should be allowed to make his own choice, as he did when he chose the profession itself. Naturally he will seek and consider advice from his teachers though he is no longer at school. He may misjudge his own ability or the scope for his particular endeavour, but he has a right to choose the road he will take. A wise man—and that could mean a young man—should recognize his limitations, but he must follow his bent. The public is aware that cardiovascular disease is predominant in human mortality. Medicine has always been influenced by public opinion, and patients will surely claim the services not only of general cardiologists but also of special cardiologists who have exceptional experience in one variety of circulatory disease.

The serious danger of specializing too early is universally admitted, and it is effectively disallowed in our institutions. But how long should the training in the sciences and in general medicine be followed after graduation? Dare I suggest that for the future specialist it may sometimes be too prolonged? Life is short. For how long should an ophthalmic surgeon restrict himself to general surgery; and for how long should a young surgeon remain in general surgery before concentrating his powers and gaining experience in cardiac surgery? Similarly, a young physician—adequately trained as such—may prejudice the fullness of his career if he postpones for too many years the plunge into what is to be his life-work. So let us give greater individual choice as to which branch of medicine he favors, and even, with

the safeguards already mentioned, as to what stage in his career he begins to specialize. I would hesitate more to make this unorthodox suggestion that specialization may begin too late if I did not know that there is often a comeback, a natural return to greater commerce with general medicine as a man proceeds in his career.

Happily there are plenty of men you cannot keep from original research, almost or actually bloodthirsty in their pursuit of it; others only need putting on the scent and they're off on "the track of truth." But must every ambitious graduate be forced by custom or authority to prosecute research in order to obtain a university post or to succeed as a practising cardiologist? Research ability used to be regarded as a rare gift, something of a phenomenon. It was search with some prospect of finding; it connoted both a spirit of curiosity and a capacity for investigation. That is not the attitude today, though one must admit that it is largely the expansion of organized research that has transformed medical practice. My question concerns the universality of the capacity for research; and I almost believe that the true investigator, great or small, is born not made. That famous literary physician, Sir Thomas Browne, wrote: "Every man is not a proper Champion for Truth, nor fit to take up the Gauntlet in the cause of Verity." Here is a matter of policy and procedure in our profession which will have to be decided. In my view we encourage good men, inapt at original research, to sacrifice their time and energy upon it when they should be perfecting themselves as bedside physicians. Are we losing our sense of proportion, exhilarated by the wonderful products of recent and current research? Is a born investigator a superior being to a born clinician and teacher? He may or may not be. Advances in medicine comprise two separate stages: first, the discovery of something new and valuable as a result of investigation; secondly, the application of that new discovery to the benefit of the individual patient. The same man may not be the right one for both stages, though he can be.

Though commoner than aptitude for research, the power to apply new (and old) knowledge judiciously is not given to everyone. It also requires a gift, namely, clinical judgment. This will ripen to clinical wisdom only by constant association with the sick. Young physicians of this type, so badly wanted, need to keep themselves abreast of the world literatu e in their specialty, and devote time to postgraduate clinical work at other centers and in other lands. Must they invariably be forced to shorten the time required for this large purpose to participate in minor and often ephemeral research before they are considered for any important staff appointment as a teacher or consultant? Not every young physician or cardiologist should be under compulsion to prosecute individual research in order to succeed.

It would not be surprising if the magnitude and the magic of recent advances went to our heads. The secret places of the heart are probed or rendered visible. The blood is directed where it may run, and under orders when it may clot; now even its channels are to be kept clear of their silt. But after all, scientific truth is discovered, not created by us; and knowledge is not always progress. Some will remember the warning given by Professor Laubry at the European Congress in 1952 about the peril of technical dogmatism and the need to retain a measure of salutary doubt. There is always a limit to scientific certainty in medicine, and some humility of approach is therefore becoming. In fact, it is probable that we are producing both truth and error as our forbears have done. The circus theory of auricular fibrillation, for example, seems to have come and gone, but happily no patient has been allowed to suffer from this physiological disaster!

The original worker in research is fully aware of the importance of his subject, and cannot be held back. Are we as aware of the immediate importance of that other pressing duty, that of applying the safest and soundest treatment to the sick of today? I mean getting it applied more certainly and more universally. If our minds are possessed by the greater things research will do for them in the problematical future, we may be less mindful of the mass of human illness requiring our best endeavor today. The vision of new truth should not blind

us to our bounden duty as doctors. Any hospital may be proud of the amount of research being conducted within its walls. But it should be equally proud of a reputation for applying—in current practice to the patients under its care—the sum of accumulated knowledge, the best treatment in the world today. In this connection may I venture the opinion that the governing bodies of teaching hospitals would be wise to retain on their staff, and value the services of, an adequate number of practicing physicians. These should not be sacrificed at the altar either of science or of uniformity, with loss to medical education and to the community. Indeed, a medical staff will never be uniform, and the establishment should always be flexible enough to fit the exceptional individual and the late-developer, and to take full advantage of any new, perhaps unexpected, discovery.

I have touched on several problems for which, I doubt not, solutions will be found or will naturally emerge. Meanwhile we must be prepared for change, willing to allow our younger gifted men freedom to strike out on their own lines according to personal inclination and judgment. The call is to adapt ourselves to the changing form that cardiology is taking rather than to attempt to maintain its earlier compactness, or to keep a strict symmetry in our organization. If only we cultivate the good feeling that has filled the cordial air of this congress, we need have no fears for the future. Most of all, the bond of unity will continue to lie in the grandeur of our purpose, namely, the prevention, relief, and cure of cardiovascular disease.

When one speaks of unity and of leadership, your thoughts will go at once to our president himself, Dr. Paul White. Friendship for a country rests largely on personal friendships with its citizens. On that basis, though not solely, I would pay my tribute to the lead taken by the United States in the realm of cardiology, and also give thanks for the close friendships which have bound me to this great country. I have been blessed by a long and firm friendship with Paul White. We spoke earlier of hero worship, and he remains one of my abiding heroes. A counterpart to Osler in medicine, he has been an ambassador of goodwill and good hope to cardiologists all over the world. He has made many original contributions, and by means of his famous book he has proved a trusty unseen consultant to countless doctors. In it he has reverently combined a choice of the past with the best of the new. By kindly understanding and enthusiasm he has inspired men wherever he has gone. His qualities of character and judgment place him high in our esteem; and that extends to his Wife whom we all admire. Paul White has gained the favor and affection of us all, and in him we possess an ideal leader in the world of contemporary cardiology.

For my third and last subject, it is my pleasure to say a little about the course of cardiology in France in recent years. Following Potain there has been an unfailing sequence of distinguished cardiologists among French physicians. First came pure clinicians like Merklen and Huchard, but it was the work of Vaquez, who combined the traditional French "clinique" with the physiological methods and researches of Marey and François Franck, that marked the beginning of contemporary French cardiology. Apart from Laubry himself, to whose achievements I will return, we record with admiration the fine influence of Clerc, the brilliant observations of Gallavardin of Lyons, in clinical cardiology, and the example of Giraud. Then I would draw your attention to the constancy and the quality of the work of Professor Lian, a physician remarkable for his clinical discernment. These have been followed, in strength, by Soulié, Lenègre, Froment, Heim de Balsac, Routier, and others.

Inspired by the work of Helen Taussig and Blalock, and by their auspicious visit to Paris in 1947, Professor Donzelot and Professor d'Allaines, physician and surgeon, have combined in the last few years to make an important contribution from the cardiac center at *l'hôpital Broussais*. This year, that work has been published by their brilliant co-workers, in particular Heim de Balsac, as a *Traité des maladies congénitales*, a large volume richly illustrated and perfectly produced. That is

true also of another up-to-date French treatise for reading and reference, *Électrocardiographie clinique* by Lenègre and his colleagues.

The contributions of France would be more widely evident today if it were not for the unfamiliarity of the English-speaking countries with that graceful language. We should all gain by a hearty understanding with France, *une entente cordiale médicale*. The place of France in the civilized and cultural world cannot be shaken by the passing effects of war or by political vicissitudes.

Too often Paris has been solely a place for sight-seeing and gaiety, and that was largely true in my own case. On an early visit, however, I was privileged to go round the wards with the great Vaquez who was attended most devotedly by his *chef de clinique*, no other than Laubry himself. As Bedford has said, "The great traditions of the Paris school of cardiology have been handed down in direct line from master to pupil for over a century, starting with Corvisart and passing in turn to Bouillaud, to Potain, to Vaquez, and finally to Laubry." Tradition may be a source of strength and a justification for authority. To Laubry was bequeathed that authority and we realize today how valuable it has proved for the continuity of French cardiology under the trials of recent years. Notice that he has been content to make this branch of medicine his life work, and the Chair of Clinical Cardiology in the University of Paris was created for him.

To begin with, he has been a brilliant clinical teacher, directly influencing students and graduates from the whole continent of Europe and elsewhere. Lenègre has described those fascinating bedside clinics by the *Patron* as reaching the unity and the charm of a cardiological ballet—though he allows that sometimes there might also be a display of fireworks!

Then since 1936 he has been the Director of the *Archives des maladies du coeur*, founded by Vaquez in 1908. In the following year, he founded the French Society of Cardiology. Lastly, he has steadily contributed original research by way of clinical intuition and synthesis combined with precise laboratory methods. The work of his pupils bears testimony to his leadership and the important theses produced year after year under his direction indicate the scope of his interests and his capacity for guidance. His son, Dr. Pierre Laubry, has also made valuable contributions.

Professor Laubry has methodically assembled his vast knowledge in book form. In 1921, he published with Pezzi, a treatise on congenital heart disease. In 1924 appeared his famous *Leçons de séméiologie cardiovasculaire*, and in 1930 his large textbook on Heart Disease. One of his favorite subjects has been gallop rhythm on which he wrote, with Pezzi, a valuable monograph. Interested by Vaquez and Bordet in cardiac radiology, he instituted with Chaperon a long and painstaking research on the radiological anatomy of the heart and great vessels, normal and pathological, using radio-opaque injections. The results appeared in two large volumes in 1939, *Radiologie clinique du coeur et des gros vaisseaux* by Laubry in collaboration with Cottenot, Routier, and Heim de Balsac. It has provided a scientific basis for cardiovascular radiology; in particular, the composition of the vascular pedicle and the lung root shadows was elucidated; and you will remember his concept of the small aorta—large pulmonary artery. In 1950 appeared the second edition of *Les maladies des coronaires* with Soulié, a comprehensive and modern textbook. In the same year, to the amazement of those who had not appreciated the depth of his scholarship, for he carries his learning lightly, came his own translation into French of William Harvey's *De Motu Cordis* (1628). We in Britain especially value this tribute from one we are proud to number among the Fellows of the Royal College of Physicians which the illustrious Harvey himself adorned.

The outcome of a man's life may be measured by the ratio between his natural gifts and opportunities, and the service that he dedicates to the common good. You will agree that it is not only his talents but the use he has made of them that has won for Professor Laubry this unique position in the cardiological world. He possesses all the elements of greatness, and

they are still manifest after an unusual experience in living, for he has passed his eightieth year. Yet his personal and persuasive charm has never left him; he is full of fun and can display the puckishness of a Churchill—and incidentally many of his other qualities. He is not only happy himself but he has the power and the will to communicate that happiness to others. In this respect we associate with him his gracious and essential companion, Madame Laubry.

In his long pilgrimage Professor Laubry, by teaching, research, and personal example, has set himself to quicken and confirm progress in the wide realm of cardiovascular disease, so that he has provided a veritable pattern of leadership. At this Laubry Lecture, on behalf of all members of this Congress, I assure him of their constant respect and affection, and express to him their grateful thanks for a full life devoted to the service of humanity.

Treatment of Cardiac Arrest and Slow Ventricular Rates in Complete A-V Heart Block

Use of Molar and Half Molar Sodium Lactate: A Clinical Study

By SAMUEL BELLET, M.D., FRED WASSERMAN, M.D. AND JEROME I. BRODY, M.D.

Molar and half-molar sodium lactate was efficacious (a) in restoring the heart beat following episodes of cardiac arrest, (b) ventricular standstill occurring during repeated Stokes-Adams seizures and (c) in increasing the idioventricular rate in the presence of complete A-V heart block. The increase in rate was related to the rapidity and amount of injection. These effects were associated with an increase in blood pressure and other evidences of improvement in the clinical state. No ventricular extrasystoles or other dangerous types of ectopic rhythms were observed in these subjects. The possible mechanisms by which the sodium lactate produces these effects are discussed.

THERE are few dependable drugs available for increasing the ventricular rate in complete A-V heart block, during prolonged sinus pauses, and following periods of cardiac arrest occurring in association with anesthesia and other states. Epinephrine[5, 9, 19, 20] (and occasionally other sympathomimetic drugs) and Isuprel[19] are used to increase the idioventricular rate, but are not always dependable and may, at times, manifest serious untoward effects. In states where the slow heart rates are associated with increased vagal tone, a wider spectrum of drugs are available; i.e., parasympatholytic drugs (atropine,[3] Banthine[14] and sympathomimetic drugs (ephedrine,[8] Paredrine[6] and others). The cardiac slowing that occurs under many conditions (medical and surgical) may, however, be the result of a combination of several factors: namely, depression of the conducting tissue in the cardiac muscle, varying degrees of increased vagal tone, or a combination of both factors. In such cases, the drugs mentioned above will be either ineffectual or only partially effective.

Although sodium lactate (molar, half molar and sixth molar) has been used for the treatment of acidosis of various etiologies,[10, 11, 12, 13, 22, 23, 24] the direct cardiac effect in the intact animal and human subject have as yet been little studied. Some of these, we feel, are of considerable practical importance and are the subject of this report.

The object of this presentation is to report the effects of sodium lactate (molar and half molar) solutions: (a) in restoring ventricular beating during repeated episodes of cardiac standstill of Stokes-Adams seizures; (b) during episodes of cardiac arrest of other etiologies; (c) in increasing the ventricular rates in states accompanied by slow heart rates; e.g., varying grades of partial A-V heart block and sinus bradycardia; and (d) in increasing the rate of ventricular beating in complete A-V heart block. These effects have, insofar as we know, not been previously reported.

EFFECT OF SODIUM LACTATE UPON EPISODES OF CARDIAC STANDSTILL DURING A STOKES-ADAMS ATTACK

Case 1. A. I., a 71-year-old white male, was admitted to the Graduate Hospital of the University

From the Division of Cardiology, Philadelphia General and Graduate Hospitals and the Robinette Foundation of the University of Pennsylvania.

This work was aided by a grant from the Foundation for Cardiovascular Research and the National Heart Institute, United States Public Health Service Grant No. H-141-D.

Dr. Wasserman is a Fellow of the Heart Association of Southeastern Pennsylvania.

The sodium lactate employed in this investigation was kindly supplied by the Eli Lilly Company of Indianapolis, Indiana.

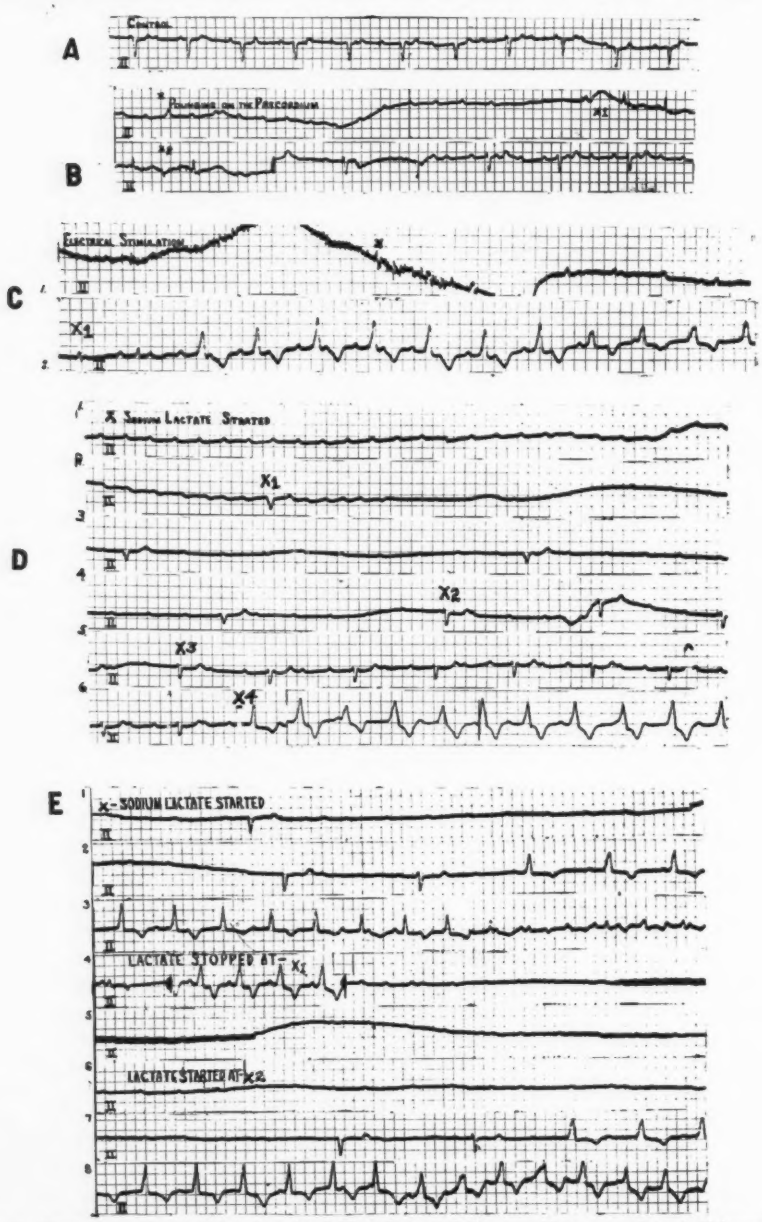

FIG. 1. Case 1. A—Control tracing, lead II, taken at 3:30 p.m. Note complete A-V heart block: auricular rate, 115; ventricular rate, 55 per minute. B—Effect of pounding on chest in presence of ventricular standstill. Pounding on chest started at X. Note beginning of ventricular beats at X1 and restoration of cardiac beating with complete A-V heart block at X2. This sequence of events was typical in restoration of the heart beat following many episodes of ventricular standstill. C—Effect of electrical stimulation. Electrical stimulation was applied at X. Note the resumption of ventricular beating at X1. The idioventricular rate is 61 per minute and is slightly more rapid than the control (rate 55 per minute) and the ventricular complexes are more aberrant. D—Following a period of ventricular standstill at X, sodium lactate was started (see text). Note the beginning of idioventric-

of Pennsylvania on Oct. 15, 1954 following a syncopal attack. While attending the outpatient clinic on Oct. 15, 1954, he suddenly lost consciousness at 11:30 a.m. During the approximate 30 second interval of unconsciousness, no pulse could be felt and no heart sounds were audible. Breathing ceased and he developed a cadaveric pallor. Pounding on the chest restored the heart beat and this was followed by resumption of respiration. He was admitted to the medical ward at about 12:30 p.m. An electrocardiogram on admission showed a complete A-V heart block (fig. 1A). The blood pressure was 124/60, the heart was top normal in size; no murmurs were audible, the apical rate was 32 per minute and slightly irregular. No congestive phenomena were present.

At about 4:15 p.m., four hours after admission, the patient became cyanotic and his heart stopped beating again. Vigorous pounding on the precordium restored the heart beat and a few seconds later, respiration began. The patient was cold and clammy and the blood pressure was 80/50. He was given nasal oxygen and ephedrine sulphate, 25 mg. (grain 3/8) hypodermically, at this time. At about 4:30 p.m., an intravenous infusion consisting of 4 cc. of Levophed in 5 per cent dextrose in water (1000 cc.) was started. The above measures were apparently not efficacious in preventing further seizures, since the heart again stopped beating at about 5:00 p.m. Thumping on the precordium again restored the heart beat. At this time, the intravenous infusion was changed to 1000 cc. of 5 per cent dextrose in water with 10 mg. of Neosynephrine. In spite of this treatment, the heart beat stopped after about 20 minutes and was again restored by a vigorous thump over the precordium. Because the patient's condition was gradually deteriorating and the cyanosis becoming more marked, at 8:30 p.m. an electric stimulator (Burdick) with DC current was used to restore the heart beat. This was successful in initiating ventricular beating in much the same manner as precordial thumping (fig. 1C). In spite of these measures, however, the periods of asystole became more frequent and the patient's clinical state gradually deteriorated. Up to this time (9 p.m.) Neosynephrine solution and atropine, 2.4 mg. (grain 1/25) had been ineffectual in maintaining the heart beat. The only procedures of value, but of temporary efficacy, had been pounding over the precordium and electrical stimulation to the chest wall.

At 9 p.m., 120 cc. of molar sodium lactate was added to the 250 cc. of intravenous fluid (making about a third molar solution). This was infused in about 30 minutes and the heart beat was restored almost immediately (in one to two minutes) after the administration of the fluid. With more rapid infusion, the ventricular beating became more rapid and increased to 78 per minute. The complete A-V heart block was maintained (fig. 1D). From 9:30 p.m. to 10:50 p.m., 250 cc. of half molar sodium lactate was given by slow drip. During this period, when the lactate was stopped the ventricular beating also stopped. To satisfy ourselves that the lactate was the sole cause of restoration of the ventricular beats, this procedure was repeated 10 times during this period of one hour and 20 minutes. The ventricular beats regularly ceased about two to five minutes after the lactate was stopped, and were immediately restored by the administration of the sodium lactate solution. At about 10:55 p.m., however, when the solution was stopped, the patient's heart rate was maintained spontaneously at about 40 per minute for approximately one hour. The patient's condition at this time was good. There was no cyanosis and the blood pressure was 150/100. At 11:55 p.m., ventricular beating ceased again and was restored by the sodium lactate solution. The same sequence of events recurred at 2:00 a.m. on October 16 with a similar result. The ventricular beating was then maintained by the administration at intervals of the sodium lactate solution until 6:05 a.m. At approximately 6:10 a.m. on Oct. 16, 1954, the patient suddenly expired. He was not receiving sodium lactate at the time of death. During the night of October 15 and 16, the following laboratory studies were obtained:

	CO_2 vol.%	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg%
10:55 p.m.	38	130	5.2	97	—
1:00 a.m.	38	128	6.0	96	10

Comment. Ephedrine sulphate, Neosynephrine, and atropine had no apparent effect in preventing or alleviating the attacks of ventricular standstill occurring in this patient. Because this patient's condition deteriorated rapidly, thumping on the chest was tried and

ular beats at X1, which increase in frequency at X2. Note the return to complete A-V heart block with QRS complexes that resemble the control at X3. As the lactate was infused more rapidly, note increase in idioventricular rate with increasing aberration of the QRS complexes. E—Shows typical effect of administration of lactate during repeated "episodes" of ventricular standstill after ventricular beating was restored. Sodium lactate started at X after a period of ventricular standstill. Note increase in idioventricular rate, which becomes more rapid with increasing speed of lactate administration. The infusion was stopped at X_1 in strip 4. Note the recurrence of ventricular standstill. Sodium lactate was started again at X_2 in strip 6. Note resumption of idioventricular beating in strip 7, reaching its maximum rate in strip 8 (75 per minute).

successfully restored cardiac contraction. Thumping on the chest wall was a consistently successful method of therapy but the response was brief and the procedure had to be repeated at increasingly shorter intervals (from 15 to 5 minutes). The same success and shortcomings were present with electrical stimulation. Furthermore, this was always accompanied by a transient, tonic convulsive seizure. Half molar lactate consistently restored ventricular beating on 10 different trials and uniformly tended to increase the idioventricular rate when administered. The increase in rate depended on the amount and rapidity of administration. In the initial phase of its effect, the heart rate was maintained only during the administration of sodium lactate. After the first two hours, the heart rate was maintained for one to four hours even after cessation of the medication. This patient experienced numerous periods of cardiac standstill during the 18 hours of observation with resultant damage to the vital centers and heart during these episodes. The latter were undoubtedly contributory factors to his final demise.

Effect in Terminal Cardiac Arrest: Restoration of Cardiac Beating with Sodium Lactate

Case 2. B. C. was a 57-year-old Negro woman who was admitted to the Graduate Hospital of the University of Pennsylvania in a comatose state on Nov. 3, 1954. The patient had been followed in the Hypertension Clinic of this hospital for several years because of headache attributed to benign essential hypertension. The blood pressure had ranged from 200/90 to 250/120. The patient had complained of severe headache in the right frontal area of the skull approximately 24 to 36 hours prior to admission. Two hours before admission, she suddenly lost consciousness and at the same time developed involuntary movements of her right arm and leg and urinary incontinence.

On admission, blood pressure was 180/100; pulse was 100 per minute (regular) and respiration was 30 per minute. The patient had a left hemiplegia and was deeply comatose, failing to respond to even painful stimuli. The heart was slightly enlarged to the left. A diagnostic spinal puncture yielded grossly bloody cerebrospinal fluid with an opening pressure of 260 mm. H_2O. The hemoglobin and red blood cell count were normal. Urinalysis revealed a 3 plus albuminuria, a 4 plus glycosuria and a positive test for ketone bodies. The fasting blood sugar was 265 mg. per 100 cc.; Carbon dioxide, 50 volumes per 100 cc. and blood urea nitrogen 14 mg. per 100 cc. The patient was started on oxygen, antibiotics and parenteral fluids. The blood sugar promptly dropped to 132 mg. per cent without insulin and remained at about that level until she died. The clinical diagnosis was hypertension with cardiac enlargement, left ventricular hypertrophy and cerebral hemorrhage.

On Nov. 5, 1954, sodium was 137 mEq. per liter, potassium 3.4 mEq. per liter, chlorides 100 mEq. per liter, carbon dioxide 52 volumes per 100 cc. and the blood urea nitrogen 18 mg. per 100 cc. The patient's temperature slowly rose from 100.8 F. rectally on admission to 102 F. on Nov. 5, 1954 and her respiratory difficulty increased. She was digitalized intravenously with a lanatoside-C preparation without improvement and at 12:30 a.m. on Nov. 6, 1954 an emergency tracheotomy was performed. Her blood pressure had dropped to 80/40 prior to tracheotomy and intravenous Levophed was necessary to maintain a blood pressure of 100–110/80–70. At 2:05 p.m. on Nov. 6, 1954, the patient's respiration ceased and the heart sounds, blood pressure and pulse were unobtainable. Thirty seconds later, 17 cc. molar sodium lactate was injected intravenously over a period of about one minute. Toward the end of this period, the heart sounds became audible and the electrocardiogram recorded a rate of 150 per minute (fig. 2A). Manual respiration was then begun and several minutes later, positive pressure respiration was instituted. The heart rate remained constant at 150 beats per minute with a blood pressure of 80/60 (fig. 2A). It appeared that this rate would be maintained indefinitely without further administration of sodium lactate; 12 minutes after artificial respiration was stopped. At 2:47 p.m., the grade of block increased to 2 to 1 with a ventricular rate of 36 per minute (fig. 2D). Sodium lactate was started soon afterwards when complete A-V heart block ensued (2E). There was a gradual increase in the idioventricular rate to 60 per minute after about 50 cc. of the molar sodium lactate solution had been given. The complete A-V heart block persisted although the ventricular complexes assumed a more normal configuration (fig. 2F). After 70 cc. of molar sodium lactate, the ventricular rate increased to 70 per minute. Since the heart rate was maintained at this time, further sodium lactate was stopped. (Two minutes prior to fig. 2G.) At about 3:00 p.m., artificial respirations were stopped and a slower idioventricular rate developed (fig. 2G). The Neophor was started again (3:10 p.m.) and the sodium lactate given (fig. 2H). This resulted in a gradual increase of the idioventricular rate (fig. 2I).

The heart rate again maintained itself at 36 per minute even after the sodium lactate had been stopped for five minutes. Artificial respiration was then stopped and the heart rate again slowed. Administration of sodium lactate without artificial

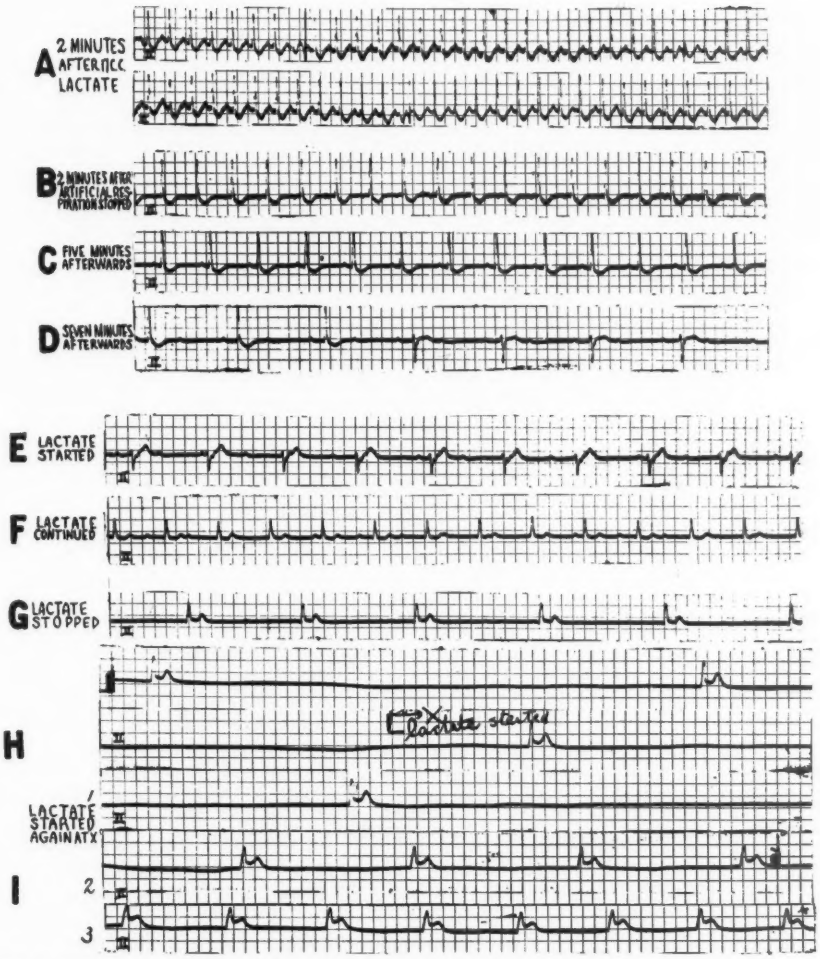

FIG. 2. Case 2. Effect of molar lactate following episode of cardiac arrest (see text). A—One minute after cardiac standstill occurred, 17 cc. of molar sodium lactate was administered in 30 seconds. (Tracing taken 2 minutes after lactate). Note return of ventricular beating at a rate of 150 per minute. This rate appeared to continue indefinitely during the maintenance of artificial respiration. B—After artificial respiration stopped for two minutes. Note the slowing of the ventricular rate and the appearance of a coronary sinus rhythm. C—Five minutes after artificial respiration stopped. Note further cardiac slowing; ventricular rate is now 68 per minute. D—seven minutes after respiration stopped. Note still further slowing of the heart. A 2:1 A-V heart block is present. The ventricular rate is 36 per minute; auricular rate is 72 per minute. E—After sodium lactate started. Note the increase in the ventricular rate to 45 per minute with complete A-V heart block. F—Note further increase in ventricular rate to 68 per minute. Complete A-V heart block is still present. G—After lactate was stopped. Note progressive decrease in heart rate. The auricular complexes are of small amplitude. H—Shows a slow idioventricular rhythm. Sodium lactate was started at X. I—two minutes after lactate was started in conjunction with artificial respiration. Note increase in ventricular rate to 12 per minute (strip 2). Strip 3. Ventricular rate now 35 per minute. The heart continued to beat for five minutes longer during lactate administration and stopped soon after its cessation.

respiration resulted in a speeding of the rate. There was sudden stoppage of the heart beat at 3:50 p.m.

Comment. After a period of cardiac arrest lasting about 30 seconds, the heart beating was restored following the intravenous administration of 17 cc. of molar sodium lactate. When the heart beat had been restored and artificial respiration started, the heart appeared to continue to beat indefinitely with a systolic blood pressure 80 mm. Hg. Inasmuch as complete recovery was impossible due to extensive and irreversible brain damage, the effect of sodium lactate administration was, therefore, studied following the anoxia induced by respiratory arrest. Sodium lactate was efficacious in increasing the rate of ventricular beating after three successive periods of anoxia which occurred when the artificial respirations were stopped. Each successive episode required larger amounts of lactate and, after the third episode, a slow idioventricular rhythm occurred from which the patient did not recover. Although the lactate increased the rate to 68 per minute, there was no change in the inherent rhythm, (complete A-V heart block). The ventricular complexes became increasingly widened with the third episode of anoxia and, although the sodium lactate speeded up the rate, death ensued with sudden cardiac standstill.

Cardiac Arrest: Temporary Resumption of Cardiac Beating Following Intracardiac Injection of Molar Sodium Lactate

Case 3. W. J. was a 47-year-old Negro man who was admitted to the Graduate Hospital of the University of Pennsylvania with carcinomatosis on Nov. 12, 1954. Toward the terminal part of his illness he manifested a marked degree of cachexia with ascites, pleural effusion, hepatomegaly and splenomegaly and was in a state of shock for 24 hours before death. His respiration stopped at 11:40 a.m. on Dec. 2, 1954. The heart continued to beat for a few minutes as noted in the continuous strips of figure 3A and B. At X2, cardiac standstill was recorded. At X3, a needle was inserted into the left ventricle. Since this procedure yielded two ectopic beats, no sodium lactate was infused until the tracing showed continuous cardiac standstill. At X4, 40 cc. of molar sodium lactate was injected slowly. Note the appearance of aberrant ventricular beats, in figure 3F; after a second intracardiac injection of 20 cc. of molar sodium lactate, these became more frequent in strips G and H. Ventricular fibrillation occurred shortly thereafter. The patient did not receive any form of artificial respiration during the period of observation. The mechanical effects of the intracardiac injection cannot be ruled out as an explanation for the restoration of the ventricular contractions.

Comment. In this, as well as in two other cases, sodium lactate was given by intracardiac injection several minutes after the respirations had ceased (none of these three patients received positive pressure artificial respiration) and cardiac beating had stopped. Although there was temporary restoration of the heart beat, there was no effect on the blood pressure or other evidence of consistent or sustained improvement. We have not had the opportunity to study the effects of intracardiac injection under more favorable circumstances.

Effect of Lactate in Complete A-V Heart Block

Effect in Presence of An Extremely Slow Heart Rate (15 per minute) accompanied by a State of Shock

Case 4. J. B., age 59, a truck driver, was admitted to the Philadelphia General Hospital on Dec. 9, 1954 with the chief complaint of "heart trouble." The patient had experienced shortness of breath and episodes of distress in the chest following exertion for the past two years. During the past 18 months, these had become particularly severe. Treatment consisted of digitoxin, aminophylline and other diuretics. For three days prior to admission, the patient experienced several attacks of syncope followed by palpitation, anorexia and generalized weakness. He had vomited "a little." The past medical history, social history and family history were unobtainable.

Examination revealed a normally-developed, pale, sweating white man who was restless, dyspneic, in shock and obvious acute distress. The temperature was 98.6 F. The blood pressure was unobtainable. There was a bruise over the right forehead, probably the result of a fall. Venous distension and pulsations were noted in the neck vessels. Decreased fremitus was present at the right base posteriorly and bilateral moist rales were heard below the seventh intercostal space posteriorly. The point of maximum impulse was located in the sixth intercostal space at the anterior axillary line. A grade III to IV rough systolic murmur was heard at the base of the heart which was transmitted into the right side of the neck. A short, soft, aortic diastolic murmur was heard best at the second left intercostal space. The aortic second sound was markedly diminished in

FIG. 3. Case 3. Effect of intracardiac molar sodium lactate during episode of cardiac standstill. A—Respiration ceased at X. Note coronary sinus rhythm, rate 50 per minute, at end of strip. This and the following strips represent a continuous tracing. B—X2. Note episode of cardiac standstill which lasted one minute. C—Number 22 needle placed in left ventricle. Note two premature beats at X3 probably the result of stimulation by the needle. No sodium lactate injected at this point. D—Further period of standstill. E—40 cc. of molar sodium lactate started at X4. F—Note return of occasional ventricular complexes. G—Note increase in ventricular rate, with bizarre ventricular complexes. H—Number 22 needle reinserted into left ventricle at X5. At X6, 20 cc. of molar sodium lactate was injected. Ventricular fibrillation occurred soon afterwards.

intensity. The liver was palpable below the right costal margin.

Because of a very slow heart rate (15 per minute on the electrocardiogram) and the shock-like state, the patient was given 120 cc. of molar sodium lactate intravenously at about 11:40 a.m. The infusion was given over a period of approximately 8 to 10 minutes. This resulted in an increased heart rate and the clinical picture of shock began to disappear. The blood pressure gradually increased to 140/95. The patient became more alert and more comfortable. A total of 240 cc. of molar sodium lactate was given in a period of 30 minutes. Following this, half molar sodium lactate was given by drip and the speed of administration regulated according to the response of the patient's heart rate (fig. 4). The solution was then given continuously from 12:30 p.m. to 5:30 p.m. at which time, it was discontinued. A total of 960 cc. of sodium lactate (360 cc. molar and 600 cc. half molar) was given in a period of five and one-half hours. At 5:30 p.m., the patient developed normal sinus rhythm with first degree A-V heart block (fig. 5). The patient appeared to be markedly improved; the blood pressure was sustained at about 140/95. The patient's urinary output was fairly constant at about 50 cc. per hour. Because of the hyperpotassemia (the serum potassium drawn shortly after admission was reported later in the day as 7.3 mEq. per liter) he was also given 1000 cc. of 5 per cent glucose in water with 15 units of insulin at 6:00 p.m. In addition, he received 2 Gm. of calcium gluconate by vein at 6:00 p.m. and 15 Gm. of cation-exchange resin orally. At 7:30 p.m., on Dec. 9, 1954, the patient's blood pressure was 146/52, the pulse rate was 72 per minute and of good volume.

On Dec. 10, 1954 the patient's urinary output decreased to 4 cc. per hour, the pulse dropped to 40 per minute and the patient became dyspneic. The blood pressure was 158/76. The electrocardiogram at this time revealed very bizarre complexes followed by ventricular flutter and ventricular fibrillation. Death ensued within a few minutes thereafter. Intracardiac epinephrine (1 cc. of 1:1000 solution) was given without effect. The patient was pronounced dead at 2:45 p.m.

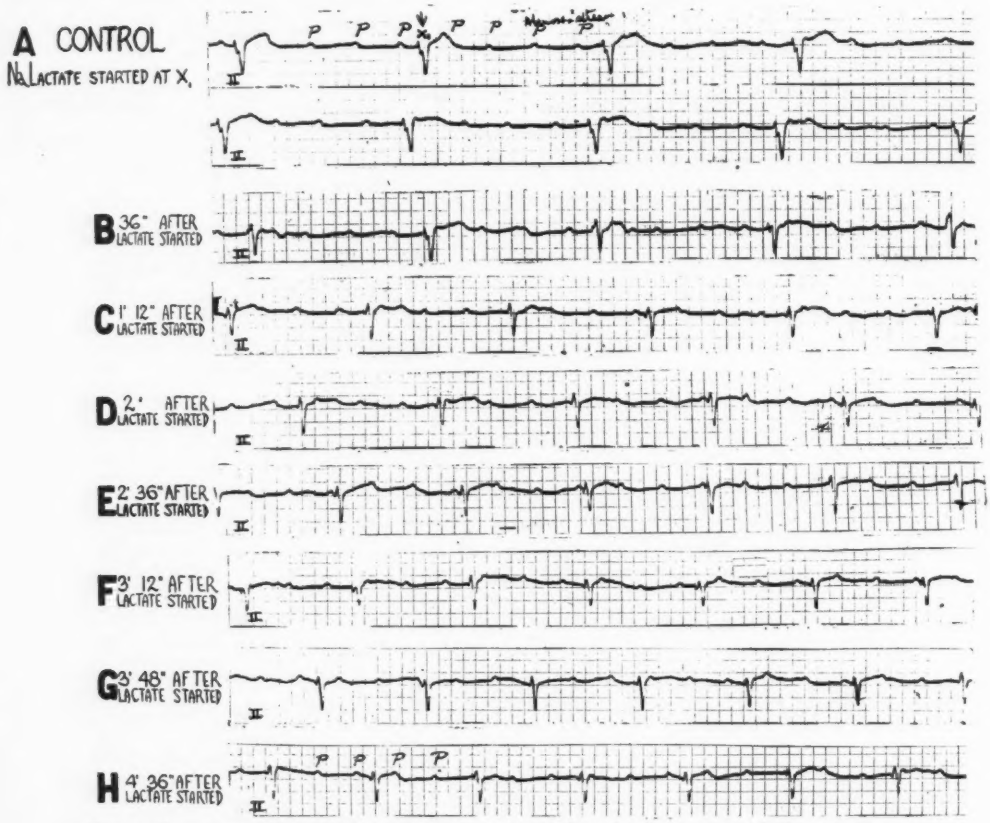
A CONTROL
No. LACTATE STARTED AT X,
B 36" AFTER LACTATE STARTED
C 1' 12" AFTER LACTATE STARTED
D 2' AFTER LACTATE STARTED
E 2' 36" AFTER LACTATE STARTED
F 3' 12" AFTER LACTATE STARTED
G 3' 48" AFTER LACTATE STARTED
H 4' 36" AFTER LACTATE STARTED

FIG. 4. Case 4. A—Control electrocardiogram (read II), taken at 11:35 A.M. Ventricular rate is 15 per minute, auricular rate is 80 per minute. Note the QRS complexes (0.18 second). Lactate infusion began at X_1. Strips taken from continuous electrocardiographic tracing. B—Thirty six seconds after lactate was started, approximately at 11:40 A.M. C—One minute and 12 seconds after lactate was started. D—Two minutes after lactate was started. E—Two minutes and 36 seconds after lactate was started. F—Three minutes and 12 seconds after lactate was started. G—Three minutes and 48 seconds after lactate was started. H—Four minutes and 36 seconds after lactate was started. Note that the ventricular rate has increased from 15 in A to 38 per minute in H, that the auricular rate has increased from 88 in A to 100 in H, and that the QRS width has decreased from 0.18 to 0.14 second. Complete A-V heart bock is still present.

The results of the laboratory studies made on December 9 and 10 follow:

	12-9-54 (After 120 cc. of molar sodium lactate)	12-10-54 (No sodium lactate for 15½ hours)
BUN mg./%	72	108
Blood sugar mg./%	86	—
NA mEq/L	137	138
K mEq/L	7.5	3.4
Cl mEq/L	90.9	94.0
Ca mg./%	7.2	8.6
CO_2 vol. %	25	63

Necropsy. The findings of interest were referable to the heart and lungs. The heart weighed 1000 Gm. and showed evidence of both right and left ventricular hypertrophy. The aortic valves were thickened, rigid and calcified and indicated the presence of aortic stenosis. In the right auricle an organized mural thrombus was present. The right lung showed evidence of an acute infarction and the main branch of the right pulmonary artery showed a fresh embolus. The pathologic diagnoses were rheumatic heart disease, aortic stenosis and insufficiency, right and left ventricular hypertrophy and acute cor pulmonale. Death was apparently caused by acute pulmonary embolism arising from the thrombus in the right auricle.

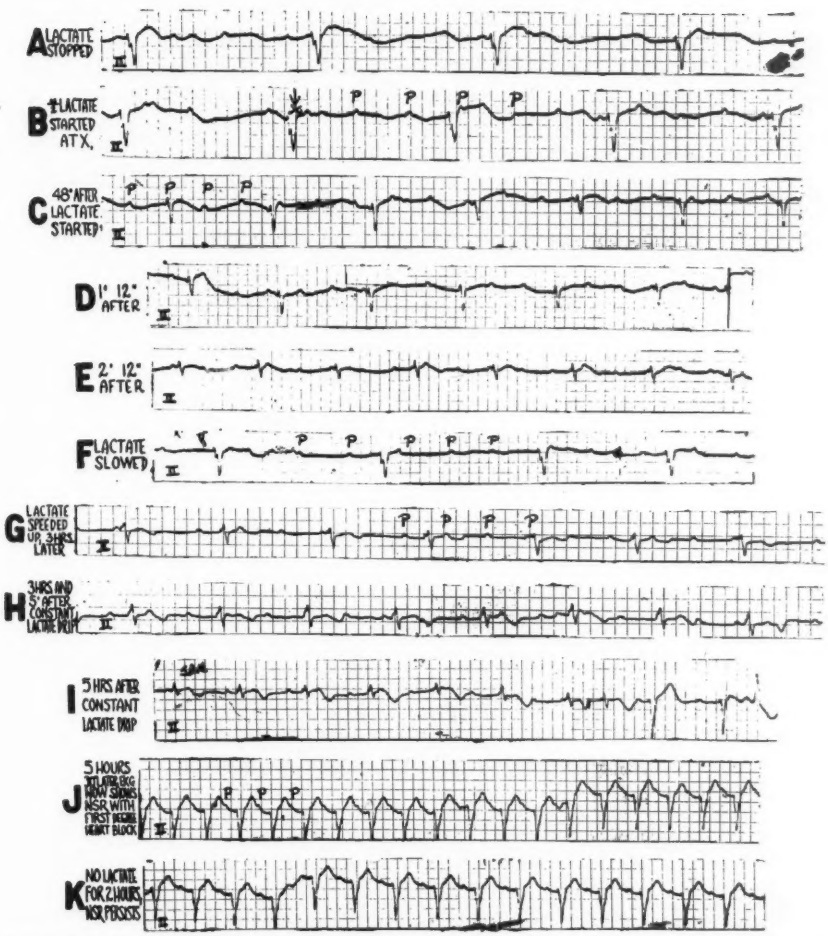
A LACTATE STOPPED
B ½ LACTATE STARTED AT X,
C 48" AFTER LACTATE STARTED
D 1' 12" AFTER
E 2' 12" AFTER
F LACTATE SLOWED
G LACTATE SPEEDED UP, 3 HRS. LATER
H 3 HRS AND 5' AFTER CONSTANT LACTATE DRIP
I 5 HRS AFTER CONSTANT LACTATE DRIP
J 5 HOURS
K NO LACTATE FOR 2 HOURS

FIG. 5. Case 4. A—Lactate was then stopped (at approximately 12:15 p.m.). A total of 240 cc. molar sodium lactate given. Note return of ventricular rate to its original low figure (15 per minute) and the return of widened QRS complexes, similar to that of the control (fig. 4A.). B—Half molar sodium lactate started at X1. (approximately 12:30 p.m.). C—Forty eight seconds after sodium lactate infusion was begun. Note increase of ventricular rate to 33 per minute and the narrowing of the QRS complexes. D—One minute and 12 seconds after lactate infusion had been started. Ventricular rate 33 per minute. E—Two minutes and 12 seconds after lactate infusion started. Ventricular rate 38 per minute. F—Lactate infusion slowed to 20 drops per minute in attempt to titrate speed of administrations against patient's heart rate. Note once again the return to slow ventricular rate (15 per minute) and widened QRS complexes (0.18 second). QRS width 0.18 sec. G—Subsequent to titration attempt, lactate was again speeded up. This tracing taken approximately three hours after continuous sodium lactate infusion. Note the more rapid ventricular rate and the narrowed QRS complexes. Ventricular rate 38 per minute. H—Three hours and five minutes after continuous sodium lactate administration. Ventricular rate, 43 per minute; auricular rate, 100 per minute. I—Five hours after lactate administration. Note more rapid ventricular rate, 48 per minute, auricular rate 110 per minute. J—Five and one-half hours after continuous sodium lactate administration. Patient now has normal sinus rhythm with a first degree A-V heart block. Sodium lactate was subsequently discontinued. The ventricular rate is 100 per minute. The QRS complexes have changed somewhat in configuration. The QRS width is 0.14 second, the P-R interval is 0.28 second. K—Two hours after cessation of sodium lactate infusion. The patient remains in normal sinus rhythm. The ventricular rate is 75 per minute; P-R is 0.28 second.

Comment. This patient, when first seen, showed a ventricular rate of 15 per minute with complete A-V heart block and bundle branch block (QRS 0.18 second). In addition, he was in a state of shock and the blood pressure was unobtainable. Within several minutes after the sodium lactate was started ventricular rates increased and the QRS complexes narrowed (fig. 4D to H). During continued administration the ventricular rate increased to 38 per minute and the auricular to 100 per minute and the QRS width narrowed to 0.14 second. Atropine sulphate, 0.8 mg. (grains 1/75) given intravenously, resulted in no significant effect on the heart rate.

The sodium lactate solution was instrumental in increasing the idioventricular rate, narrowing the QRS complexes, elevating the blood pressure, and reversing the state of shock. That the sodium lactate solution was responsible for this improvement was indicated by the fact that on three successive occasions, cessation of administration or marked slowing of the rate of infusion resulted in a return to the control tracing; that is, a decrease of the ventricular rate to 15 per minute, widened QRS complexes and a fall in blood pressure (fig. 5A). On resumption of sodium lactate administration, the process was reversed. Following five hours of continuous sodium lactate administration, the increased heart rate and blood pressure were subsequently maintained without additional lactate infusion. Indeed, the heart rate tended to gradually increase spontaneously and at 5:30 p.m. normal sinus rhythm appeared associated with a partial A-V heart block (fig. 5).

It is of some interest to consider the mode of action of the sodium lactate in this patient. The decrease in acidosis, increase in the idioventricular rate and increase in blood pressure were accompanied by an improvement in the clinical state. These factors were probably also instrumental in improving the hyperpotassemia. The serum potassium the following day was normal (3.4 mEq. per liter).

Effect of Sodium Lactate upon the Auricular and Ventricular Rates in a Case of Asymptomatic Complete A-V Heart Block

Case 5. M. F., a 38-year-old white woman, was admitted to the Philadelphia General Hospital on Oct. 14, 1954 with the diagnosis of rheumatic heart disease, aortic valvular disease and complete A-V heart block. The auricular and ventricular rates preceding and following sodium lactate are shown in

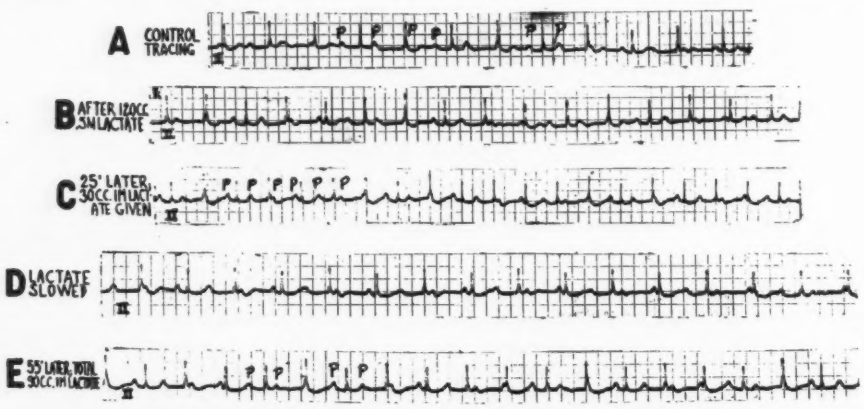

Fig. 6. Case 6. Effect of lactate on the auricular and ventricular rate in complete A-V heart block. A—Control tracing. Note complete A-V heart block. Ventricular rate 71 per minute; auricular, 100 per minute. B—Note slight increase in auricular and ventricular rates. Ventricular rate 79 per minute; auricular 107 per minute. C—After 25 minutes an additional 30 cc. of molar sodium lactate had been given. Note the ventricular rate of 100 per minute and auricular rate of 150 per minute. D—After sodium lactate administration was slowed. Note decrease in auricular and ventricular rates. E—Fifty-five minutes after the initial infusion had been started. Ninety cc. of additional molar sodium lactate given.

table 1. It should be noted that the control rates of the auricles and ventricles were 100 and 71 per minute, respectively (fig. 6A). Ten minutes after the administration of half molar sodium lactate (initial infusion) and immediately following the administration of 30 cc. of molar sodium lactate (second infusion), the auricular and ventricular rates speeded up to 150 and 107 per minute, respectively. This maximum rate was attained when the solution was infused rapidly at a rate of 150 drops per minute (fig. 6C). As the rate of infusion was slowed, the ventricular rate slowed correspondingly (fig. 6D). Ten minutes after the end of the infusion, the atrial and ventricular rates had returned to 115 and 78 per minute, respectively, or to a figure slightly above the control values. There was no effect on the inherent or basic rhythm (complete A-V heart Block). This patient experienced paresthesias (numbness and tingling of the hands and feet and about the mouth) at the height of the lactate effect. These manifestations could have been the result of the alkalosis and slight hypocalcemia that resulted during the infusion.

TABLE 1.—*Effect of Sodium Lactate on the Auricular and Ventricular Rate in Complete A-V Heart Block (Case 5)*

Sodium Lactate Given	No. of cc.	Time (p.m.)	Rate per Min.	
			Auricular	Ventricular
Control	—	2:15	100	71
0.5 molar solution	120	2:25	107	79
0.2 molar solution	120	2:35	115	83
Total	240			
1.0 molar solution	20	2:40	140	88
1.0 molar solution	30	2:45	150	100
1.0 molar solution	20	2:55	134	100
1.0 molar solution	20	3:10	124	88
Total	90			
		3:20	115	78

Effect in Complete A-V Heart Block, with Occasional Cycles of Normal A-V Conduction: Conversion to 2:1 A-V Heart Block by Molar Sodium Lactate

Case 6. L. W., a 69-year-old Negro woman, was admitted to the Philadelphia General Hospital on October 26, 1954 with the diagnosis of arteriosclerotic heart disease. The control electrocardiogram showed complete A-V heart block with a ventricular rate of 42 per minute, consisting of idioventricular beats and occasional QRS complexes which appeared to be normally conducted (fig. 7A, complex X). Serum electrolytes (sodium, potassium, chloride and carbon dioxide combining power) were normal.

After 100 cc. of molar sodium lactate the complete A-V heart block and idioventricular heart beats were entirely replaced by normally conducted ventricular complexes and a 2:1 A-V heart block ensued (fig. 7B). About 15 minutes after the sodium lactate was stopped, the electrocardiogram returned to the control tracing: namely, complete A-V heart block with idioventricular beats.

Effects of Sodium Lactate in other Arrhythmias and Conduction Disturbances

The effects of sodium lactate have been studied in patients with partial A-V heart block, in the presence of sinus bradycardia with nodal escape, in the slow heart rate accom-

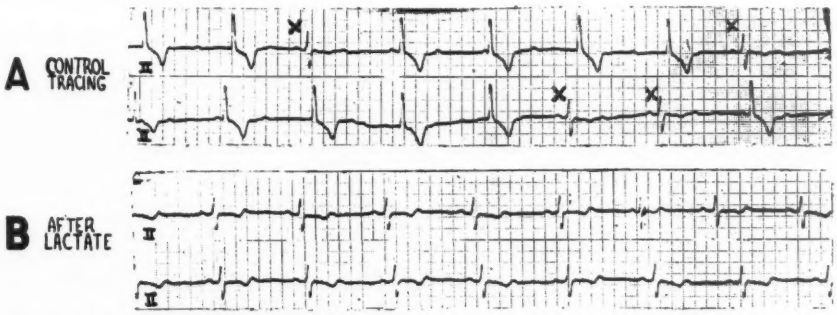

FIG. 7. Case 6. Effect of molar sodium lactate on complete A-V heart block with occasional normally conducted beats. A—Control. Note presence of complete A-V heart block, auricular rate 73 per minute; ventricular rate 42 per minute. An occasional normally conducted beat is seen at X. B—After the administration of 100 cc. of molar sodium lactate. Note the occurrence only of conducted beats with the presence of 2:1 A-V heart block.

panying hyperpotassemia, bundle branch block and in patients with extrasystoles.

In addition, the effects on the electrocardiogram, blood pressure and serum electrolytes have been studied in normal human subjects. This data will form the basis of a subsequent report.[5]

Discussion

Method of Administration and Dose of Molar and Half Molar Sodium Lactate

Although sixth molar sodium lactate (isotonic solution) has been rather commonly employed in the therapy of acidosis, the use of molar or half molar sodium lactate has been rather infrequent. The latter solutions have been used by Hartman,[10, 11, 12] Neubauer[22, 23, 24] and others for the treatment of acidosis in the human subject due to various factors; diabetic acidosis, the acidosis of renal origin, acidosis due to diarrhea, and acidosis accompanying severe infections. Hartman[12] (1938) injected 3.2 to 8.1 cc. of molar sodium lactate per kilogram of body weight intravenously in a period of 18 to 27 minutes; 0.125 per cent calcium chloride was added to prevent tetany. Neubauer used 120 to 240 cc. of sodium lactate, administered as molar or half molar solution over a period of 1 to 2 hours in the treatment of acidosis associated with azotemia; 2 to 6 Gm. of calcium gluconate was given within three to four hours after the lactate to prevent tetany secondary to the alkalosis. Sodium lactate, especially prepared for oral administration, has also been employed for mild cases in conscious patients.[22]

We employed a dose ranging from 15 cc. of molar sodium lactate* administered in about one minute, to a total of 960 cc. (molar and half molar solution) administered within a period of five hours. The rapidity of injection depended upon the urgency of restoring the heart rate. For example, in case 1, the initial dose of 250 cc. of third molar sodium lactate solution was injected rapidly within about 30 minutes. In case 2, 15 cc. was injected in one minute; in case 4, 240 cc. in four minutes was required to increase the heart rate from 15 to 60 beats per minute. After the rate had been restored the infusion was given more slowly, at the rate of 50 to 100 drops a minute, to maintain the heart rate close to a normal figure. It is interesting that in these cases the rapidity of the heart rate varied directly with the speed of infusion and could be regulated by it. In case 1, after an infusion period of approximately two hours, the heart was maintained for long periods of time (four to five hours) without further administration during the period; in case 4, after an injection period of five hours, the heart rate was maintained without further sodium lactate administration.

* Each 100 cc. of the solution as supplied contained sodium lactate, 11.2 Gm., representing 11.2 per cent (w/v). In terms of potential alkali it equals 8.4 Gm. (approximately 130 grains) sodium bicarbonate.

Electrolyte Alterations and Fate of Sodium Lactate

When given in a dose of 7 cc. of the molar sodium lactate solution per kilogram over one-half hour, it has been demonstrated[12] that sodium r-lactate is completely metabolized within a period of from one to two hours by normal individuals. A portion of the lactate radical is oxidized and the remainder converted into glycogen.

The lactic acid concentration increases in the blood and reaches a concentration of 120 mg. per 100 cc. in one hour after the injection of 220 cc. of molar sodium lactate[12] and usually returns to a normal level within one to two hours after the injection is started. In the treatment of acidosis, even though lactic acid may be abnormally high before the sodium r-lactate injection, normal values are usually seen two or three hours after the injection. This has been explained as being due to the effect of the increased blood flow on the utilization of lactic acid.

Abramson and coworkers[1] pointed out that injected lactate acts like an easily oxidizable substrate which replaces other food stuffs in metabolism. A point of considerable interest is the fact that the metabolism of sodium lactate may be accomplished up to the point of death. In a case reported by Hartmann and Senn,[13] although the patient died about four hours after the administration of sodium lactate, the plasma carbon dioxide content had

increased from 27.5 to 44.6 volumes per 100 cc. during the first half of this period. Similar cases have been documented by these authors.

The sodium ion, liberated during the oxidation of lactate or its conversion into glycogen, is transported to the kidneys for excretion largely as the bicarbonate salt. There exists, therefore, a state of alkalosis of the base bicarbonate excess type for several hours after the injection with commensurate increase in the hydrogen ion concentration of the blood. Within four hours, more than half of the injected sodium is excreted. Serum chloride levels show a reciprocal drop with the elevated carbon dioxide combining power.[12]

An increase of from 25 per cent to 50 per cent above the basal rate of oxygen consumption follows the intravenous administration of the racemic sodium lactate to normal human subjects when given at a rate of 7 cc. per kilogram of bodyweight. This increase is apparently the result of the oxidation of the d-isomer.[12] The blood sugar increases slightly and then sinks to slightly hypoglycemic levels. The intravenous administration of sodium lactate results in a significant increase in maximum tubular excretory capacity for para-aminohippuric acid in man. The average maximum increase amounted to about 30 per cent of the preinjection levels.[17]

Mechanism of the Cardiac Effect

Theoretical Considerations. The mechanism of the observed cardiac effects of sodium lactate are not entirely established. Nevertheless, there are certain actions of the solution and its breakdown products that have been well documented and which merit discussion. These actions will be discussed under the following headings: effect of the lactate; effect of the alkalosis or reduction in degree of acidosis; the action of the sodium ion; the sympathomimetic effect and the vagolytic effect.

Effect of the Lactate. The lactate which is relatively rapidly utilized serves as a fuel which can be readily utilized by the heart. There results an increase of 20 per cent to 50 per cent in the basal rate of oxygen consumption. There is some evidence that the heart muscle can utilize lactate for direct provision of energy. Bing[4] found that the isolated dog's heart removed from the circulating blood more lactic acid than any other substance and that lactate is utilized for direct combustion. An increase in arterial lactate levels caused an increase in myocardial lactate extraction. However, compared with glucose, the myocardial lactate extraction and usage were usually significantly lower. The lactate may act directly as added substrate to the Krebs cycle and may be converted to pyruvate via the coenzyme diphosphopyridine nucleotide, circumventing the intermediate steps of conversion of glucose to pyruvate. This may, in effect, serve to act directly in the oxidative metabolic mill of the Krebs cycle and to more efficiently utilize and conserve the energy of the cell.

Effect of the Alkalosis. There is considerable evidence which indicates that alkalosis has a profound effect on maintaining and accelerating the heart beat: i.e., that acidosis tends to retard and alkalosis tends to accelerate conduction. Ringer[26, 27, 28] (1882–83), in the isolated perfused heart, observed that when a ventricle had lost its contractility it could be restored for a short time by adding to the dose of saline 5 cc. of sodium bicarbonate solution. That the sodium bicarbonate acted by virtue of its alkalinity and not as a sodium salt was indicated by the fact that the addition of calcium hydrate or ammonium carbonate produced the same restoration of beats. Ringer[28] felt that sodium bicarbonate exerted little, if any, influence over the cardiac contractions; this was regulated by the action of calcium and potassium salts. The effect of sodium bicarbonate was that of neutralizing the acid reaction produced by the contraction; without this neutralizing effect the tissue and blood would become acid resulting in cessation of function. Mines[18] (1912), working on the isolated terrapin and the mammalian heart, observed that electrical and mechanical excitation decreased with an acid pH and the A-V intervals were lengthened and disappeared with a pH of 7.0. Shifting to a high pH reversed this process. He was of the opinion that with a fall in pH, the total excitatory processes develop more slowly and that a rise

in pH results in a more rapid development of the excitatory process, acceleration rhythm and increase in conductivity.

Andrus and Carter[3] (1924) reported effects on the P-R interval in a perfused terrapin heart similar to that reported by Mines. The rate at which the excitation was transmitted in auricular muscle was dependent upon the hydrogen ion concentration of the perfusate; it was increased by more alkaline and decreased by more acid pH. The administration of sodium lactate is accompanied by relatively rapid alterations in pH. This probably occurs earlier in the region of the heart even before it is reflected in the peripheral blood. As a result, any local changes characterized by acidosis in the heart would tend to become less marked and the balance would proceed towards the alkalotic state. Since anoxic states are frequently accompanied by acidosis, these local changes in the heart would tend to speed up the rate. That alkalosis is an important factor of itself is indicated not only by the experiments performed in the isolated heart, but also by the fact that changes of a similar type were obtained by the use of sodium bicarbonate during the complete heart block produced by obstructive asphyxia in dogs.[5]

Effect of Sodium. Injection of molar sodium lactate results in an increase in the serum sodium concentration. The sodium liberated from the lactate is excreted by the kidneys as the bicarbonate salt. Within four hours, more than half of the sodium is excreted in this way. That the increased sodium content of the extracellular fluid effects the conductivity in the cell is supported by many observations.[15, 16, 21] Hodgkin and Katz[15] (1949), using the giant axon of the squid, showed that the action potential was abolished by sodium-free solutions and that a decrease in the sodium concentration decreased the height of the action potential. The height of the action potential was increased by a hypertonic solution containing additional sodium chloride. The rate of rise of the action potential was directly proportional to the external concentration of sodium. The conduction velocity undergoes a substantial decrease in solutions of low sodium content. Increasing the external potassium causes a depression of both acting and resting potential. Natsuk and Hodgkin[21] stated that the reversed potential difference across that active membrane was related in linear fashion to the logarithm of the sodium concentration in the external fluid.

Hoffman, Siebens and Brooks[16] determined the effect of alterations in sodium on the excitability of cardiac tissue before and after vagal stimulation. When the sodium concentration was decreased, both the magnitude and rate of rise of the action potential are diminished. It has been suggested on the basis of these effects that acetylcholine, by decreasing the sodium entry, causes a slower heart rate and decreased rhythmicity at a time when repolarization is accelerated.

Sympathomimetic Effects. There is considerable evidence to suggest that molar or half molar sodium lactate does not possess typical sympathomimetic effects. The lack of these effects is suggested by the failure of lactate to increase the blood pressure or the heart rate in the normal human subject in the doses given and even in large doses in the dog. Rapid administration of sodium lactate in the dog results in a fall in blood pressure.[5] There was no significant increase in the heart rate in the normal experimental animals. Although sodium lactate restored the heart rate in cardiac arrest and increased the ventricular rate in complete A-V heart block, it did not produce extrasystoles and other dangerous types of ectopic rhythm as are frequently observed with epinephrine.

Vagolytic Effect. That sodium lactate may have at least a partial vagolytic effect is suggested by (a) the increase in the auricular rate in the complete and partial A-V block,[5a] (b) decrease in the P-R interval; (c) increase in the ventricular rate in partial A-V heart block.[5a] Although preliminary experiments suggest that its vagolytic effects in doses of 100 cc. to 200 cc. in the human subjects are not particularly marked, evidences of some vagolytic effect have been shown in the dog.[5]

Summary of Mode of Action. We cannot state with certainty at this time the mechanism by which the molar or half molar sodium lactate produces the effects noted. At the present time

we are attempting to more definitely localize the site of action in increasing the heart rate (cases 1 to 4) and in narrowing the QRS complex in the cases studied (cases 4 and 6). Preliminary observations in the human subject and in dogs suggest that the chief effects are due to alkalosis, to the direct effect of the sodium ion and probably the lactate ion on cardiac muscle. Preliminary studies in the dog would lead us to believe that the alkalosis is the most important factor. An increase in the rhythmicity of the cardiac pacemaker and/or the conductivity of the impulse within the heart muscle may also result from a change in any of the factors compromising these properties. The mode of action would explain (a) restoration of the heart beat after cardiac arrest and ventricular standstill; (b) change of the widened QRS complexes to those that are narrower (cases 4 and 11); and (c) the increase in idioventricular rate in complete A-V heart block, the increase depending upon the amount and rapidity of the sodium lactate administration.

Summary

The therapy of episodes of cardiac arrest, ventricular standstill during Stokes-Adams seizures, the slow idioventricular rhythm of complete A-V heart block, the slow ventricular rates of partial A-V heart block and sinus bradycardia by the administration of molar and half molar sodium lactate is reported.

After epinephrine, Neosynephrine and atropine were without effect in restoring the ventricular beating during repeated, prolonged periods of ventricular standstill in a case of Stokes-Adams syndrome, molar and half molar sodium lactate, administered intravenously, restored the heart beat on 10 separate occasions. After two hours the heart continued to beat spontaneously for several hours. In the case of terminal cardiac arrest the intracardiac injection of sodium lactate temporarily restored ventricular beating.

Sodium lactate was administered to three cases of complete A-V heart block. In one of these the patient presented a ventricular rate of 15 per minute, widened QRS complexes and a state of shock. Sodium lactate increased the ventricular rate to 60 per minute and increased the blood pressure to 120 to 140 systolic with resultant marked improvement in the patient's clinical state. The widened QRS complexes were significantly narrowed. Decrease in the rate of administration or cessation of administration of the lactate solution on two separate occasions resulted in a return of the electrocardiogram to the control rate of 15 per minute. After five hours of administration the ventricular rate had increased to 60 per minute and was maintained without further lactate administration. About one hour later normal sinus rhythm was restored.

In a second case of complete A-V heart block (case 5), the ventricular and atrial rates were significantly increased following the administration of sodium lactate. In a third case of complete A-V heart block, with occasional normally conducted beats (case 6), the complete A-V heart block was abolished and the idioventricular beats were entirely replaced by normally conducted beats.

Sodium lactate appears to have marked qualities of increasing cardiac rhythmicity while possessing little or no pressor action. Our observations in the human subject and in the experimental animal suggest that this solution possesses qualities that should be of help in the prevention and therapy of sudden cardiac standstill. In addition, it did not produce dangerous ectopic rhythms.

The dose, method of administration and fate of the sodium lactate in the body is discussed.

The possible mechanisms by which the sodium lactate produces the effects described are outlined.

Summario in Interlingua

Es reportate le uso de solutiones molar e semi-molar de lactato de natrium in le tractamento de episodios de arresto cardiac, de inhibition ventricular in accessos del syndrome de Stokes-Adams, del lente rhythmo idioventricular in complete bloco atrio-ventricular, de reducite frequentia ventricular in partial bloco cardiac, e de bradycardia sinusal.

Post que, in un caso del syndrome de Stokes-Adams, epinephrina, Neosynephrina, e atropina

non habeva succedite, in le curso de repetite e prolongate accessos de inhibition ventricular, a restaurar le pulso ventricular, le administration intravenose de lactato de natrium in solutiones molar e semi-molar resultava in le restauration del pulso cardiac in dece episodios separate. Post duo horas le corde comenciava batter spontaneemente lo que continuava durante plure horas. In le caso de arresto cardiac terminal, le injection intracardiac de lactato de natrium restaurava le pulso ventricular al minus temporarimente.

Lactato de natrium esseva administrate in tres casos de complete bloco atrio-ventricular. In un de illos, le patiente presentava un frequentia ventricular de 15 per minuta, allargate complexos QRS, e un stato de choc. Lactato de natrium augmentava le frequentia ventricular a 60 per minuta e le systolic pression sanguinee a 120 o 140 mm Hg, con resultante marcate melioration del stato clinic del patiente. Le allargamento del complexos QRS esseva reducite significativemente. In duo episodios le reduction o cessation del administration de lactato de natrium resultava in un retorno al previe frequentia ventricular de 15 per minuta. Post cinque horas de administration de lactato de natrium le frequentia ventricular attingeva 60 per minuta e manteneva iste valor sin administration additional del solution. Circa un hora plus tarde le normal rhythmo sinusal esseva restaurate.

In un secunde caso de complete bloco atrio-ventricular, le frequentias ventricular e atrial se augmentava significativemente post le administration de lactato de natrium. In un tertie caso de complete bloco atrio-ventricular, characterisate per le occurrentia sporadic de complexos QRS apparentemente a conduction normal, le complete bloco atrio-ventricular esseva eliminate e le pulsos idioventricular esseva completemente reimplaciate per pulsos a conduction normal.

Lactato de natrium pare haber un marcate capacitate a augmentar le rhythmicitate cardiac sin exercer multe o mesmo ulle action pressorial. Nostre observationes in subjectos human e in animales experimental pare indicar que le solution de lactato de natrium ha qualitates que promitte esser utile in le prevention e le therapia de subite inhibitiones cardiac. In plus, illo non produce periculose rhythmos ectopic.

Es discutite le dosages, le methodos de administration, e le destino ulterior de lactato de natrium in le corpore.

Le possibile mechanismos per que lactato de natrium produce le effectos describite es analysate in lineas general.

Acknowledgments

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Corticotropin (ACTH) in Heart Disease: Its Paradoxical Effect on Sodium Excretion in Resistant Congestive Failure

By Augusto A. Cámara, M.D. and Ferdinand R. Schemm, M.D.

Since the spring of 1952 we have undertaken a clinical trial of corticotropin in 21 cardiac patients with resistant edema. Of these, there were eight with arteriosclerotic, eight with chronic rheumatic, and three with hypertensive heart disease, while two had cor pulmonale. Beneficial results were obtained in 17, or 81 per cent of the cases. These consisted of a spontaneous diuresis either during corticotropin administration or after its withdrawal, or an alteration of response to mercurials, the patients subsequently responding favorably, whereas they had previously been completely refractory to the mercurial diuretics.

DURING recent years, it has been increasingly realized that a number of edematous patients fail to respond to the usual diuretic measures now in use. The picture of truly resistant edema where diuretic measures, including vigorous use of mercurial diuretics, are entirely of no avail, or cause natriuresis with no weight loss (or even a weight gain), resulting inevitably in hyponatremia, is a frustrating one. An occasional patient responds, albeit temporarily, to simultaneous administration of salt solution and a mercurial diuretic.

Since the spring of 1952, we have obtained sufficient clinical evidence and electrolyte balance data which promise to establish corticotropin (ACTH) as the therapeutic agent *par excellence* for the situation just described. This is the more fascinating if one recalls that to date corticotropin has been considered contraindicated in congestive heart failure due to its sodium-retaining effect. Well aware of its known physiologic actions at the time, we nonetheless decided to start a clinical trial of corticotropin in the following categories of patients in whom there was little to lose: (1) those cardiac patients with truly resistant edema as described above, (2) heart patients with severe myocardial insufficiency (left ventricular) in whom there was severe pulmonary passive congestion and incapacitating, unrelievable paroxysms of dyspnea and (3) cardiac patients with severe, associated intrinsic bronchopulmonary disease (asthma, bronchiectasis, emphysema).

The initial trial of corticotropin in these cardiac patients was guided by the consideration that benefit might be obtained from the action of the hormone on some organ-system of the body which would offset that concerned with sodium retention through increased production of desoxycorticosterone-like substances by the adrenal cortices. This might possibly be in the form of improvement of the myocardium. With this thought, the clinical trial of corticotropin in heart disease was launched, but not without fear and trepidation.

Method and Material

The patients reported in this paper were al treated in the Metabolic Unit of the Deaconess Hospital. On admission, the patient's height an weight were obtained and from then on dail fasting weight in the morning was recorded on scale which is sensitive to 100 Gm. The usu diuretic regimen as well as full digitalization or r digitalization were instituted from the time

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This work was done during Dr. Cámara's tenure of a Research Fellowship of the American Heart Association.

admission and intractability of edema was verified by our own observations. In several instances, control periods of observation lasting for as long as 20 to 41 days (during which vigorous diuretic measures were used) were carried out prior to institution of corticotropin therapy.

The patients, selected with the criteria previously mentioned, were carefully evaluated for the existence of contraindications to corticotropin, other than congestive heart failure. The prospective candidate was then given a Thorn test to determine the responsiveness of the adrenal cortex.

In the meantime, 24-hour urine specimens were collected daily, collections being started and ended at 6:00 A.M. and their volumes recorded. The daily urinary excretion of chloride, sodium and potassium were determined in all except two patients. The morning following admission, and again immediately before corticotropin therapy, blood specimens were obtained in the fasting state for initial chemical determinations, which included plasma sodium, potassium, chloride, carbon dioxide combining power, serum proteins, blood sugar, urea nitrogen, cholesterol, blood pH, plasma specific gravity and plasma osmotic pressure. The procedures used in these analyses have been mentioned in a previous publication.[1] The same set of determinations or part of it was obtained at appropriate intervals and at the end of treatment. Total eosinophil count was repeated on the fourth to sixth day of corticotropin therapy* to insure effective dosage of corticotropin, which was given intramuscularly in doses of 10 to 25 mg. (depending on body weight) every six hours for 10 to 12 days. Two patients (C. O. and H. W.) received corticotropin intravenously over a period of nine days, the dose gradually being reduced from 15 mg. (in three divided doses) to 5 mg. daily. One patient (A. F.) received cortisone because no circulating eosinophils were found in the peripheral blood prior to corticotropin administration.

For the calculation of electrolyte balance data, the daily dietary intake of sodium and potassium was calculated from the figures given by Bowes and Church,[2] for the food actually ingested. Losses of sodium and potassium through the urine, by emesis or by any drainage (thoracentesis, paracentesis) as well as levels of plasma sodium and potassium were determined by the use of a Beckman flame photometer. Skin and fecal losses were estimated, using the figures obtained by Arn and Steimer.[3]

Results

To date a total of 21 cardiac patients have met our criteria warranting the use of corticotropin. Of these, eight had arteriosclerotic cardiovascular disease and three had hypertensive heart disease. Of the remaining 10 patients, 2 had cor pulmonale secondary to broncho-pulmonary disease while eight had rheumatic heart disease with chronic valvulitis. The age range for the whole series was 39 to 69 years; there were 13 males and 8 females.

The clinical data on these patients are summarized in table 1.* Seventeen (81 per cent) out of the 21 patients were definitely benefited by a course of corticotropin. Of the four failures, one patient (R. H.) died of a pneumonitis which developed on the ninth day of therapy. The three other failures were all cases of chronic rheumatic valvular disease. Although they tolerated the course of corticotropin therapy well, no improvement could be discerned from the point of view of intractability of edema and incorrigible hyponatremia, even with sodium supplements (patient M. C.), or from the point of view of relief of severe left ventricular insufficiency with incapacitating paroxysms of dyspnea (patients E. S. and R. T.). One of the failures already mentioned, patient M. C., proceeded on a progressively downhill course, as she had been doing prior to corticotropin despite all the other adjuvant measures, and expired three weeks later. At autopsy a "fish-mouth" stenosis of the mitral valve was found associated with an aneurysmal dilatation of the left atrium. Two other failures mentioned above, patients E. S. and R. T., are still living, but both have suffered much in morale in the last several months, with the justifiable feeling that they have reached the stage when nothing can be done for them. The first, patient E. S., had had a "bottle baffle" operation for marked mitral valve insufficiency in Boston two and one half months previously, while the other patient, R. T., is considered unsuitable for cardiac surgery due to marked involvement of both mitral and aortic valves. She has had numerous embolic phenomena in the past, the last one to the brain, resulting in a permanent dysarthria.

The beneficial results obtained in the 17

* A quantity of corticotropin sufficient for a complete therapeutic course for 10 patients was generously supplied by Dr. G. W. Bissell of the Armour Laboratories.

* At the request of the Editor, table 1 is being omitted. This table will be furnished on request.

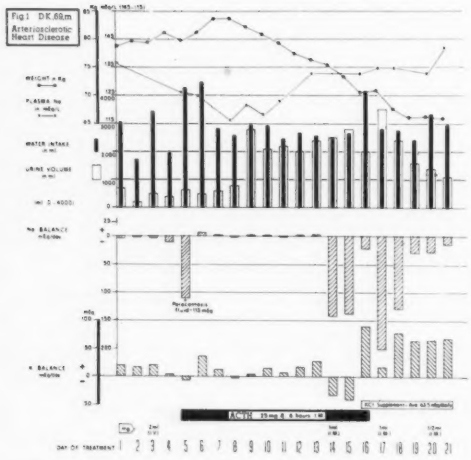

FIG. 1. Clinical and Laboratory Data on patient D. K., male, age 69 with arteriosclerotic heart disease.

patients may be grouped together into the following categories:

(1) Spontaneous diuresis (i.e. without the use of a mercurial diuretic) occurring *during* and continuing after the course of corticotropin in four patients (D. K., F. R., R. B. and C. O.), with loss of previously resistant edema. In two of these patients (D. K. and F. R.), the initial diuresis was mainly a *water* diuresis, with correction of a coexisting hyponatremia (no sodium supplements being given), followed by proportionate sodium and water loss until all signs of edema disappeared.

(2) Diuresis occurring spontaneously *after* discontinuation of corticotropin, with edema weight loss and relief of intractable pulmonary passive congestion in three patients (R. D., E. M. and R. V.).

(3) An altered response to mercurial diuretics, the patients responding effectively whereas they had been refractory to them previously; this change occurring either *during* or after the course of corticotropin therapy. This type of beneficial effect was observed in the majority of cases, as exemplified by patients R. M., C. M., R. C., B. S., A. F., W. R., H. L., R. H., C. B., and H. W.

Graphic representations of pertinent data on a few of the patients illustrate vividly the different types of beneficial results obtained with corticotropin. The graphs are self-explanatory. In representing sodium and potassium balance data, columns *above* the base line show *positive* balance, while those *below* the base line indicate *negative* balance.

Patient D. K., the data on whom are represented in figure 1, had had a myocardial infarction eight years previously. For two and one-half years he had been in congestive failure, the edema responding at first to the usual measures but gradually and progressively becoming intractable. He came with the history of nonresponse to various diuretic measures including the intravenous injection of mercurial diuretics three times a week. On admission he presented the picture of anasarca with severe hepatic passive congestion (lower edge of the liver was 4 inches below the right costal margin), moderate ascites, and orthopnea with Cheyne-Stokes respiration. A trial period longer than four days on our usual regimen was not attempted on account of the rapidly worsening condition of the patient. There was persistence of marked oliguria and development of more edema, abdominal distention, persistent hiccups, and severe hyponatremia.

Corticotropin was started on the fifth hospital day, and note in figure 1 that on the fifth day of corticotropin therapy, after an initial weight gain of 3.9 Kg. and a drop of plasma sodium to 116 mEq. per liter, there started a continuing diuresis which, in the brief span of 13 days, resulted in a total edema weight loss of 17.8 Kg. Calculation of data from the fourth to the tenth day of corticotropin administration during which an edema weight loss of 8.2 Kg. occurred, shows that there should have been a negative sodium balance of 1,033 mEq. (8.2 × average plasma sodium concentration of 126 mEq. per liter). The total urinary sodium output during those six days amounted to only 4.3 mEq., and there was a *positive* sodium balance of 3.7 mEq. The absence of a natriuresis during the first five days of increased volume of urine output is interesting, especially since it was accompanied by a progressive rise in plasma sodium concentration. Clinical improvement went hand in hand with the rapid clearing of edema, ascites and hepatic passive congestion. The small doses of Thiomerin were subsequently given to shorten his hospital sojourn, the patient being eager to rejoin his family in Canada. We feel that the diuresis would have continued anyway, perhaps at a slower rate, had the mercurial diuretic not been given.

The data on patient R.D. are graphically represented in figure 2. This 69-year-old physician had suffered an acute myocardial infarction seven months previously and had been subsequently readmitted to the hospital twice previously for severe pulmonary passive congestion prior to these studies. For about four weeks before this admission he had been incapacitated by severe, unrelievable paroxysms of

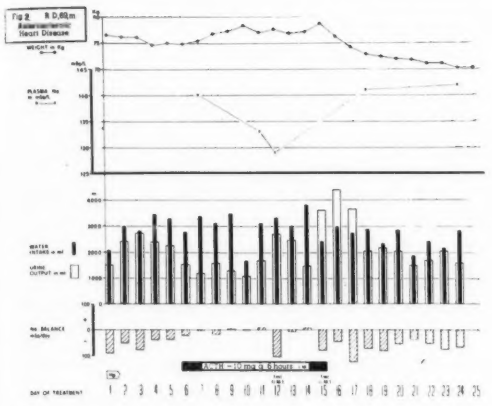

FIG. 2. Clinical and Laboratory Data on Patient R. D., male, age 69, with arteriosclerotic coronary heart disease.

dyspnea. He manifested marked Cheyne-Stokes respiration on admission. The lower two-thirds of the lungs were full of moist rales. Peripheral edema was minimal. Nevertheless, there was a total edema weight loss of 8.5 Kg. following the discontinuation of corticotropin. As seen in figure 2, small doses of Thiomerin were given twice, on the seventh and again on the tenth day of corticotropin. There was a rather pronounced, uninterrupted natriuresis following the last day of corticotropin.

The problem in patient R. D. was not an intactable edema, but rather, the severe paroxysms of dyspnea. Following the course of corticotropin therapy he became free of respiratory distress and was able to resume part-time practice for nine months.

Patient R. M., the data on whom are graphically represented in figure 3, had severe chronic valvular disease on a rheumatic basis, involving both the aortic and the mitral valves. She had been in auricular fibrillation for at least 21 years, and in severe congestive failure for two years before she was first seen in 1949. From then on there followed a long series of hospital admissions with a progressively intractable edema. Incidentally, she was found in 1950 to be a potassium loser and had to have daily supplements of potassium chloride.

On this admission in 1952 she was massively

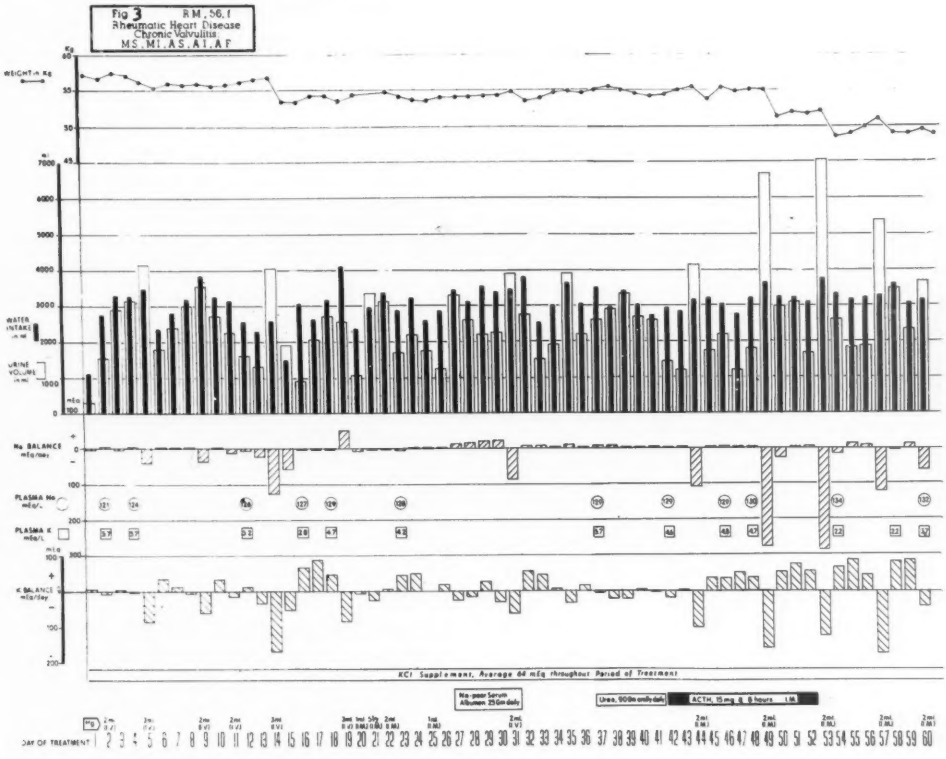

FIG. 3. Clinical and Laboratory Data on Patient R. M., female, age 56, with rheumatic heart disease, chronic valvulitis.

anasarcous, with deep pitting edema involving the upper and lower extremities, and the lower two-thirds of the torso. There were ascites and severe passive congestion of the lungs and liver. A 41-day battle with her edema, including the use of daily potassium supplements, large and rather frequent intramuscular and intravenous doses of Thiomerin, intravenously administered sodium-poor albumen, even large oral doses of urea along with all the other adjuvant diuretic measures, accomplished little. The weight loss during the precorticotropin period was only 2 3 Kg; most of this represented tissue weight loss since the average daily food intake contained only 860 calories.

Note that figure 3 shows that during and after the course of corticotropin, *intramuscular* doses of Thiomerin were much more effective in producing both water and sodium diuresis. The urine volumes were 6700 ml. and 7100 ml. when Thiomerin was administered on the eighth day of corticotropin and the day following its discontinuation, respectively, with a corresponding urinary output of sodium of 282 mEq. and 297 mEq. The subsequent weight loss of 6.6 Kg. is more significant if one takes into account that an increase in appetite with corticotropin boosted her average daily caloric intake from 860 to 1,940 calories. There was virtual clearing of peripheral edema, with persistence of only minimal ascites.

Another patient, C. M., whose response to corticotropin was similar to that of the patient described above (fig. 3, R. M.) is worth referring to. A course of corticotropin (which was given only after a control period of 22 days during which true resistance was demonstrated), resulted in complete alteration of response to mercurial diuretics. There occurred a rapid clearing of edema; he has not required mercurial injections since his discharge from the hospital, and has remained free of edema for 28 months at the time of this report.

Discussion

The results we have had with the use of corticotropin in apparently hopeless and terminal cases of cardiac patients have so far been highly gratifying. Judging from the favorable response obtained in 81 per cent of the patients, it would seem that a new avenue of hope has been opened for such patients.

Excessive renal tubular reabsorption of sodium (and the corresponding proportionate amounts of water) is generally accepted as the ultimate mechanism of edema formation. Since this function of the renal tubules is under the control of desoxycorticosterone-like substances from the adrenal cortex, the use of *corticotropin*, which stimulates adrenocortical activity, has been considered contraindicated in congestive heart failure.

From theoretical considerations it would seem logical to anticipate that the use of corticotropin would cause an intensification of the congestive failure syndrome in heart disease. We have, however, demonstrated that when the regimen which is ordinarily effective in combating edema is used in conjunction with corticotropin, the theoretically deleterious effect, perhaps observed during the initial few days of its administration, becomes relegated to the background and is then overshadowed by heretofore unsuspected beneficial effects. This regimen, which has been described in detail in previous publications,[4] is instituted from the beginning of treatment, and is maintained during and after corticotropin therapy. The patients receive an acid-residue diet which contains from 9 to 30 mEq. of sodium daily, depending on the caloric intake. Up to a certain point of dietary sodium intake, the emphasis is on the *acid reaction* of the diet residue rather than on strict sodium restriction. Ammonium chloride is administered daily in doses of 1.5 to 4 Gm.; it is given in loose powder form buffered with equal amounts of calcium carbonate in a capsule. The few patients who do not tolerate this are given the enteric coated form of ammonium chloride. Strict attention is paid to water intake which is kept between 2500 and 4000 ml. daily in the majority of cases. To accomplish this, oral water intake is supplemented with intravenous infusions of 5 per cent dextrose in distilled water, if necessary. Fasting weights are obtained daily in the morning. Those patients who do not diurese spontaneously by the fifth or sixth day, or who become distressed by the usually slight initial weight gain (maximum 3.9 Kg. observed in patient D. K.) are given intermittent doses of Thiomerin. Adjuvant measures such as digitalization, oxygen administration, sedation, and others are used as indicated. This regimen has shown its value in minimizing the initial antidiuretic effect of corticotropin, and later potentiating and maintaining its beneficial effect.

Fortunately, contraindications to the administration of corticotropin in cardiac patients warranting its use have not been encountered

with frequency in our series. When known contraindications (other than congestive failure) coexist, careful clinical judgment has to be exercised between possible catastrophe and anticipated beneficial results. Using proper precautions, no condition has been considered as an absolute deterrent to the use of corticotropin when faced with a desperate situation. Such was the case with one of the patients, F. R., (severe hypertension for 10 years; acute pulmonary edema before admission) whose condition rapidly deteriorated within a week following admission. This patient had had a chronic duodenal ulcer with a flare-up only two weeks previously, had developed an infection (pleuropericarditis) and had become markedly agitated and mentally confused, but a course of corticotropin therapy was decided on nevertheless, on account of a rapidly failing myocardium, as manifested by severe paroxysmal dyspnea with Cheyne-Stokes respiration of a marked degree, acute dilatation of the left ventricle (demonstrated by serial chest roentgenograms), marked fall in blood pressure, and finally right-sided failure with generalized edema. Precautionary measures taken included the following: daily red cell counts and hemoglobin determinations and daily examination of the stools for occult blood were done while blood was held in readiness for emergency transfusion; Probanthine was administered intramuscularly in 15 mg. doses every five hours; adequate protective doses of penicillin, streptomycin and erythromycin were given; and to combat agitation, he was sedated with intravenous doses of sodium amytal for 36 hours. The gamble taken with the use of corticotropin was richly rewarded in this case, with recovery from acute myocardial failure and since then, freedom from congestive failure and from respiratory embarrassment for seven months at the time of writing.

The clinical and laboratory detection of rheumatic activity in chronic cases of rheumatic heart disease is admittedly a difficult one. However, the absence of fever, and the other cardinal signs of activity (joint manifestations, chorea, subcutaneous nodules, and other signs), the normal sedimentation rate, the nonprolonged P–R interval by electrocardiograph, and the absence of leukocytosis all lead us to conclude with some certainty that we were not dealing with rheumatic carditis in the eight patients with rheumatic heart disease in this series. This point is brought up because of the well-known fact that cardiac decompensation from active rheumatic carditis may be corrected by corticotropin or cortisone, whereas the value of these hormones in congestive failure from the mechanical effects of chronically deformed valves has not until now been carefully evaluated. Interestingly enough, three of the four failures in this series of 21 patients were cases with chronic rheumatic heart disease.

Potassium chloride was administered orally or intravenously to some of these patients receiving corticotropin in whom negative potassium balance became manifest from increased urinary excretion of the electrolyte or from a dropping level of plasma potassium concentration. Two of the patients, R. M. (fig. 3) and R. T. had previously been known to be inordinate potassium losers, and they received daily supplementary doses of potassium chloride throughout the period of treatment. Liddle, Bennet and Forsham[5] have demonstrated that sodium retention induced by corticotropin may be corrected by the administration of large doses (200 mEq. or more) of potassium salts. They found that potassium salts in large doses consistently cause sodium diuresis, even in subjects not receiving corticotropin, although the natriuretic effect of potassium was much less in the latter than in those undergoing corticotropin therapy. Although the supplementary doses of potassium chloride in some of our patients undoubtedly contributed to their general well-being, it is unlikely that natriuresis was induced by its administration. The dose of potassium chloride was usually 40 mEq., and did not exceed 80 mEq. daily in any of our patients, a dose much smaller than that shown to produce natriuresis by the above mentioned workers. In patient R. M., potassium chloride had been given daily prior to corticotropin in the same dosage as during and after corticotropin yet the intractability of edema had persisted, and no effective natriuresis could be obtained even with vigorous use of diuretic measures until after the course of corticotropin therapy. Potassium

supplements were not given to patient D. K. (fig. 1) until the last day of corticotropin administration at which time he had already lost 13.1 Kg. of edema weight and had had sodium diuresis. There was no definite correlation between potassium administration and the start of natriuresis in the other patients studied in this series, hence it may be safely assumed that the small doses of potassium chloride administered did not play a major role in inducing natriuresis.

In 1952 Andrus and his co-workers[6] reported two patients with severe mitral stenosis in whom corticotropin therapy produced a striking improvement of respiratory function with clearing of pulmonary congestion. The depression of respiratory function seen initially in those patients was of such severity as to render mitral valvuloplasty hazardous, but following improvement with corticotropin, they stood mitral valve surgery well, and were greatly benefited thereby. No comment was made on the effects of corticotropin on peripheral edema, although it was stated that the patients did gain weight in the course of corticotropin therapy. Their studies centered mainly on the effect of corticotropin on some of the pulmonary complications of mitral stenosis, one of their main findings being a reduction of the abnormally high pulmonary artery pressure. No electrolyte studies were mentioned.

The mode of action by which corticotropin produces the salutary effects described in our report is worthy of speculation. Earle and his co-workers[7] found in normal subjects an increase in urinary sodium excretion (after an initial decrease from control values) occurring sometime between the tenth and fifteenth days of corticotropin administration. They attribute this phenomenon, at least in part, to the observed concomitant increase in glomerular filtration rate. No attempt was made in our series of patients to compare glomerular filtration rates before, during and after the course of corticotropin therapy. However, it would seem from theoretical considerations alone that such variations in glomerular filtrate volume would not cause variations in the amount of urinary sodium excreted, for, after all, the distal tubules, which have the capacity to alter their reabsorptive power within a wide range, are the final arbiters of the quantity of sodium excreted. Clinically this is borne out by the observation that nephritic patients in the nephrotic stage with massive edema may have near-normal glomerular filtrate volumes, but the daily urinary excretion of sodium may be reduced to only a fraction of a milliequivalent. Conversely, nephritic patients with moderate impairment of glomerular function may have no trouble keeping free of edema even on a diet with no salt restriction. The renal tubules do not reabsorb sodium excessively, and sodium balance is maintained.

Furthermore, Earle and his co-workers point out that the *rapidity* with which changes occurred either on corticotropin *administration* or *withdrawal* suggest that the observed alterations in filtration rate and renal plasma flow were the result of functional (i.e., constriction of the efferent arterioles of the glomeruli, associated with dilatation of afferents) rather than morphological changes. Certainly then, the remissions observed in our patients, lasting in several instances as long as nine months, and in one instance 28 months, cannot be explained on the basis of *temporary* changes in renal hemodynamics induced by corticotropin.

It may be mentioned in passing that Metcoff and co-workers,[8] in a careful study of renal function in nephrotic children in whom diuresis was induced by corticotropin, came to the conclusion that altered renal hemodynamics may be the *result* rather than the *cause* of favorable response.

Thus, the explanation for the beneficent effects of corticotropin in heart disease has to be sought along different lines. There is the possibility that corticotropin may stimulate the adrenocortical production of a hormone that has an action antagonistic to that of desoxycorticosterone, thus inducing diuresis not only after, but even *during* the course of corticotropin therapy. An effect such as this has been reported with the use of cortisone in normal subjects[9] and nephrotics. Luetscher and Deming[10] have emphasized that with cortisone in nephrotics, the sodium diuresis occurs mainly *after* withdrawal of the hormone. They attribute this phenomenon to temporary inhibition of endogenous adrenal production of de-

soxycorticosterone as a part of the overall diminution in adrenal cortical activity, induced by the administration of cortisone. Of interest is the suggestion[9, 11] that cortisone prevents the rise in levels of antidiuretic substance levels in the blood of adrenalectomized rats, although it does not reduce the amounts present in normal nonadrenalectomized animals. To explain the initial water diuresis observed in patients D. K. and F. R. with corticotropin, therefore, one would have to assume a pre-existing adrenal insufficiency with little or no production of endogenous cortisone, a condition which was presumably corrected by the administration of corticotropin.

The above explanation for the beneficent effects observed with corticotropin in congestive failure is an attractive one. It will need confirmation by further trials using cortisone. The possibility remains that corticotropin may mediate its beneficial action through other still undiscovered hormones produced by the adrenal cortex. Differences have been reported[12] between the actions of cortisone and those of corticotropin in nephrotic patients. According to Luetscher's observations, corticotropin in general is followed by an earlier and more profuse elimination of water and sometimes of sodium during treatment. The diuresis at the end of corticotropin administration is generally more abrupt and profuse than that seen after cortisone.

Lastly, one may add the possibility that corticotropin, directly or through some adrenocortical hormone, may produce an improvement of the failing myocardium primarily, thus striking at the root of the cause for the existence of an increased volume of extracellular fluid. The long duration of remissions from congestive failure in several cases, and in other instances the marked and dramatic relief of paroxysmal dyspnea and Cheyne-Stokes respiration (due to left ventricular insufficiency) seem to favor this speculation. The case of patient F. R. who was rescued from an episode of acute cardiac failure and in whom serial roentgenological chest films showed a return of myocardial tone (following acute dilatation of the left ventricle) with corticotropin affords strong circumstantial evidence which cannot be slightly put aside.

Be that as it may, it is hoped that this report will not only encourage further clinical trial of corticotropin in the manner described, but also stimulate more research in basic cardiac physiology with special reference to the pituitary and adrenocortical hormones.

Summary and Conclusions

A clinical trial of corticotropin, with detailed electrolyte and water balance studies, has been underway since the spring of 1952 in apparently hopeless and terminal cardiac patients falling into the following categories: (1) Cardiac patients with truly resistant edema in whom previous vigorous diuretic measures in our hands had produced no results, and in whom hyponatremia, hypokalemia and other electrolyte disturbances had developed with the usual methods of treatment, (2) heart patients with severe myocardial insufficiency (left ventricular) in whom there was severe pulmonary passive congestion and incapacitating, unrelievable paroxysms of dyspnea and, (3) cardiac patients with severe associated intrinsic bronchopulmonary disease (asthma, bronchiectasis, emphysema).

Of the 21 cardiac patients (eight arteriosclerotic, three hypertensive, eight chronic rheumatic, and two cor pulmonale) who thus far have met our criteria warranting the use of corticotropin, 17 (or 81 per cent) were definitely benefited by the hormone. The salutary effects may be grouped into the following types of response: (1) Spontaneous diuresis (i.e., without the use of a mercurial diuretic), occurring *during* (usually fourth to sixth day of treatment) and continuing after the course of corticotropin therapy with loss of previously resistant edema. This was observed in 4 cases. (2) Diuresis occurring spontaneously *after* discontinuation of corticotropin, with edema weight loss and relief of intractable pulmonary passive congestion, was seen in three patients. (3) An altered response to mercurial diuretics, the patients responding effectively whereas they had been refractory to them previously, this change occurring either *during* or *after* the course of corticotropin therapy. This type of response was observed in 10 patients.

Of the four failures, three had chronic valvular disease on a rheumatic basis, and one suffered from arteriosclerotic heart disease.

Five of the patients with chronic rheumatic valvular heart disease who responded favorably to corticotropin showed no clinical nor laboratory evidence of active rheumatic carditis prior to therapy.

The initial increase in edema with the use of corticotropin is minimized by the adjuvant use of a diuretic regimen which is reviewed in brief. Continued use of the same regimen after the course of corticotropin maintains and potentiates the beneficial effects of this hormone.

Speculations on the possible mode of action of corticotropin, based on our observations and studies of other investigators, lead to the tentative conclusion that cortisone or some other still undiscovered adrenal hormone, produced in response to corticotropin stimulation, may overcome by antagonistic action on the renal tubules the sodium-retaining effect of desoxycorticosterone-like substances which are also presumably produced by the adrenal cortex in response to corticotropin administration. The possibility remains, based on clinical observations, that corticotropin may, directly or through some other adrenocortical hormone, produce an improvement of the failing myocardium.

Further clinical trial of corticotropin in such patients will be carried out, while awaiting explanation of its rationale from basic research in cardiorenal physiology.

Summario in Interlingua

Ab le primavera 1952 nos ha interprendite essayos clinic con corticotropina in 21 patientes cardiac con edema resistente. Inter istes, 8 esseva arteriosclerotic, 8 con chronic morbo cardiac rheumatic, 3 con morbo cardiac hypertensive, 2 con corde pulmonal. Resultatos benefic esseva obtenite in 17 casos (81 pro cento). Illos consisteva in spontanee diurese durante o post le curso de corticotropina o in un alteration del responsa a mercuriales in le senso que post corticotropina le patientes respondeva favorabilemente durante que previemente illes habeva essite completemente refractori al diureticos mercurial.

Acknowledgment

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Serum Transaminase Levels in Experimental Myocardial Infarction

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Serum glutamic oxalacetic transaminase concentrations rise sharply after myocardial infarction produced by bead embolization of the coronary tree in the closed chest dog. The peak concentration is reached in 9 to 23 hours post injury. Rises 20 to 30 times greater than normal may be obtained and are directly correlated with the amount of infarction estimated at autopsy. Serial serum transaminase levels may provide a clinical tool to supplement the electrocardiogram in the diagnosis of acute myocardial infarction as well as provide a roughly quantitative estimate of the amount of myocardium involved.

CLINICAL and laboratory studies performed on human subjects have shown that the serum level of glutamic oxalacetic transaminase rises significantly following acute myocardial infarction.[1, 2] However, in order to determine the relationship, if any, between serum transaminase levels and amount of infarcted muscle in clinical cases, careful pathological studies will have to be made on autopsy material over a span of many years. Therefore, it was decided to attempt to determine the nature of this relationship in experimental animals.

By utilizing the method of Agress and his associates,[3] graded experimental infarction was produced in dogs. Then, a quantitative estimation of infarcted muscle at autopsy could be correlated with any changes in serum transaminase level.

Methods

Fourteen dogs weighing an average of 20 Kg. (range 19 to 29 Kg.) were used. Intravenous Nembutal was chosen as the anesthetic. Two dogs were used as sham operated controls. The remaining 12 dogs were subjected to coronary embolization with plastic microspheres. By this method, a steel catheter is passed through the left carotid artery into the ascending aorta of the closed chest dog, and plastic microspheres are injected into the coronary ostia after occlusion of the aorta by inflation of a special balloon.

Control serum samples were taken on all dogs before and one hour after the introduction into the aorta of the catheter used in the embolization technique. Spheres were then injected into the coronary arteries until S-T depressions in the electrocardiogram appeared. Previous studies have shown that when persistent S-T segments shifts occur following coronary embolization with plastic microspheres, infarction has been produced.[3] This point was taken as the time of injury. The dogs were kept under light anesthesia and serum samples were withdrawn one hour post injury and every four hours thereafter, for the first 24 to 36 hours on nine dogs. Three dogs were observed for as long as 72 hours. These sera were shell-frozen and lyophilized. The lyophilized sera were coded and sent from the Los Angeles laboratory to the New York laboratory for serum transaminase analysis. The serum transaminase levels were determined by the method of LaDue, Wróblewski and Karmen.[1, 2]

At autopsy, black-and-white and color photographs were taken of the hearts before and after serial sections were made at approximately 1 cm. intervals through the left ventricle and septum (fig. 1). The amount of infarction was estimated in terms of per cent of total myocardium after gross study of the epicardial and endocardial surfaces and of the serial sections. These estimations are believed to be reliable to within 5 to 10 per cent, based on our experience with several hundred hearts of this type. It is to be noted that these estimations of the amount

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FIG. 1. Left ventricle and septum. Note discrete areas of infarction throughout myocardium—from endocardial to epicardial surfaces.

% INFARCTION	INITIAL T-A LEVEL	PEAK T-A LEVEL	PEAKTIME POST INJ.
0	60	40	0
	19	112	17 hrs.
5 - 10%	13	150	17 hrs.
	13	128	9 hrs.
	17	104	10 hrs.
10 - 20%	27	295*	9 hrs. *
	22	296	15 hrs.
	23	292	17 hrs.
20 - 30%	0	316	23 hrs.
	17	364	9 hrs.
30 - 40%	15	450	15 hrs.
	13	906	12 hrs.
50% +	16	674	13 hrs.
	14	728	20 hrs.

FIG. 2. A table illustrating the relationship between per cent of myocardial infarction, as estimated at autopsy, and peak serum transaminase level.

of infarction were made before results on the sera were obtained. The coded serum analyses were also determined without knowledge of the presence or amount of infarction. These two completely independent sets of data were then analyzed with the following results.

RESULTS

Figure 2 shows the amount of estimated myocardial infarction, the initial transaminase levels, the peak transaminase levels and the peak times post injury in hours. (The peak values are near-approximations because of the discontinuous method of serum sampling.) There was a significant rise in transaminase level in all dogs, as compared with the control values, following myocardial infarction. In

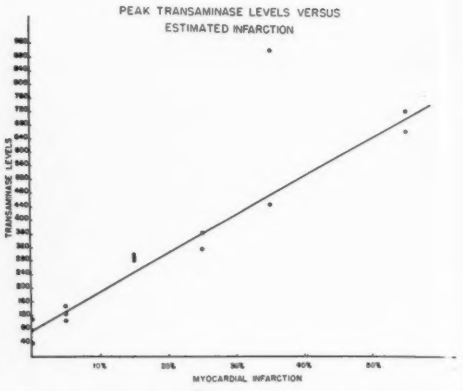

FIG. 3. Correlation between serum transaminase level and per cent of myocardial infarction.

some instances, the rises were as great as 20 to 30 times that of the control levels. Moreover, these data suggest that there is a rough correlation between the amount of infarction estimated at autopsy and the peak transaminase level.

When the amount of infarction is plotted against the peak transaminase level, a similar correlation between the two variables (fig. 3) is apparent.

The time course of serum transaminase levels is shown in figure 4. A marked rise in serum transaminase level occurs following experimental myocardial infarction in all cases. The peak transaminase level occurs between 9 to 23 hours post injury, with a decline after this point. In many of the experiments, a gradual progressive increase in transaminase level occurred after the clearly defined primary peak. The explanation for this is not yet known, but as this phenomenon also occurred in a control dog, we believe it unlikely that it can be a function of myocardial infarction. Rather, it is possibly due to the prolonged anesthesia. However, this remains to be determined by further experimentation.

The rise in serum transaminase in experimental myocardial infarction, thus confirms that seen clinically[1, 2, 4] and, in addition, the data show a semiquantitative relationship between the serum level and the amount of injured myocardial tissue. The mechanisms of the physical and temporal nature of the serum rise are not known, but it has been shown[5]

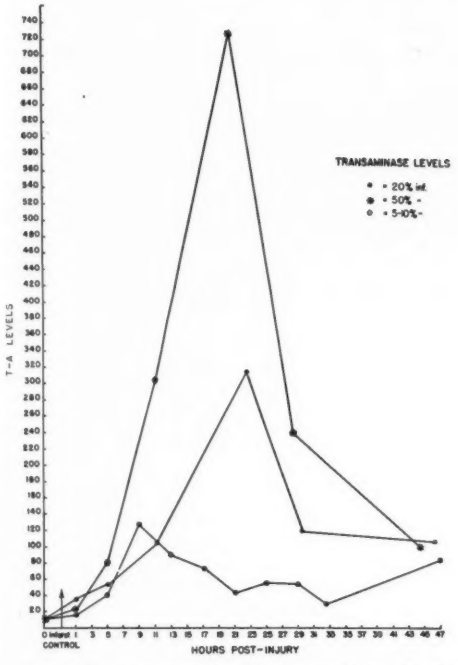

FIG. 4. Time course of serum transaminase level in three typical experiments with varying degrees of myocardial infarction.

that the transaminase level of infarcted myocardial tissue is markedly decreased from normal.

CONCLUSIONS

The results of this cross-country collaborative study in which the data were independently determined, lead to the conclusions that (1) in all cases the serum transaminase levels rose sharply after myocardial infarction, (2) there exists a relatively linear correlation between the peak serum transaminase levels and the amount of myocardial infarction as estimated at autopsy, and (3) infarction of as little as 10 per cent, and possibly less, of the total myocardium is associated with significant rises in transaminase levels.

The method of serum transaminase analysis, as developed by Karmen, Wroblewski and LaDue, is simple and quick and can be performed in most clinical laboratories. It is believed that serum transaminase determinations will prove useful as a clinical tool to supplement the electrocardiogram in the diagnosis of acute myocardial infarction, and will probably provide a roughly quantitative estimate of the amount of myocardium involved. The preliminary results are promising and deserve further study.

CONCLUSIONES IN INTERLINGUA

Le resultatos de iste studio cooperative—con datos determinate independentemente per participantes in California e New York—impone le sequente conclusiones: (1) Post infarcimento myocardiac le nivello del transaminase seral exhibi un acute augmento. (2) Il existe un correlation plus o minus linear inter le nivellos maximal de transaminase seral e le grado de infarcimento myocardiac apparente al autopsia. (3) Infarcimento de solo 10 pro cento (o possibilemente mesmo de minus que 10 pro cento) del myocardio total es associate con un significative augmento del nivello de transaminase.

Le analyse del transaminase seral secundo le methodo disveloppate per Karmen, Wroblewski, e LaDue es simple e rapide e pote esser executate in le majoritate del laboratorios clinic. Nos opina que determinationes de transaminase seral se provara utile como supplemento clinic de methodos electrocardiographic in le diagnose de acute infarcimento myocardiac. Illos va probabilemente provar se capace a fornir plus o minus satisfacente estimationes quantitative del portion de myocardio involvite. Le resultatos preliminari es promittente e merita studios additional.

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The Role of Auscultation in the Differentiation of Fallot's Tetralogy from Severe Pulmonary Stenosis with Intact Ventricular Septum and Right-to-Left Interatrial Shunt

By Louis Vogelpoel, M.B., M.R.C.P. and Velva Schrire, M.B., Ph.D., M.R.C.P.

A clinical and phonocardiographic study has been made of the murmurs and heart sounds in the differentiation of Fallot's tetralogy from severe pulmonary stenosis with intact septum and right-to-left interatrial shunt. A striking difference in the behaviour of the systolic murmur was found in the two conditions and this affords a new, simple bedside method of diagnosis. Important differences in the behaviour of the heart sounds were also found, but these are usually more difficult to evaluate clinically and may require special study.

THE value of auscultation in the diagnosis of congenital heart disease has not been sufficiently appreciated. This paper is concerned with the importance of auscultation in the differential diagnosis between Fallot's tetralogy and severe pulmonary stenosis with intact ventricular septum and reversed interatrial shunt. Accurate diagnosis is of great importance. The Blalock-Taussig operation is contraindicated for severe pulmonary stenosis with reversed interatrial shunt, whereas it has proved to be an excellent operation for Fallot's tetralogy.[1-5] The diagnosis can generally be made with a reasonable degree of accuracy from consideration of the clinical, radiological and electrocardiographic findings. However, it is often necessary to confirm the diagnosis by means of cardiac catheterisation and angiocardiography. Even with all available methods, certain difficulties arise as discussed elsewhere.[6]

Any additional, clinical differentiating sign is therefore of value and it is the purpose of this communication to present new physical signs, which will enable accurate diagnosis to be made by careful bedside auscultation. Furthermore, certain clinical and phonocardiographic observations made during the study will be presented.

From the Cardiac Clinic, Department of Medicine, University of Cape Town and Groote Schuur Hospital. This study was supported in part by a grant from the Dr. C. L. Herman Staff Research Fund, University of Cape Town.

Clinical Material and Methods

All cases accepted for this study presented the common diagnostic problem of pulmonary or infundibular stenosis associated with central cyanosis. This combination usually resolves itself into the diagnosis of Fallot's tetralogy and severe pulmonary stenosis with reversed interatrial shunt. Pulmonary stenosis with rare associations such as transposition of the great vessels, single ventricle and tricuspid atresia were excluded from this study.

Eighteen cases of Fallot's tetralogy and six cases of severe pulmonary stenosis with intact ventricular septum form the basis of this study. All cases had central cyanosis. Cases were accepted only if cardiac catheterisation, selective angiocardiography, intravenous angiocardiography or necropsy proved (a) whether severe pulmonary valvular or infundibular stenosis was present and, (b) whether the ventricular septum was intact or not. If the right-to-left shunt took place in the ventricle through a ventricular septal defect and over-riding aorta, then Fallot's tetralogy was considered proven. If it was established that the ventricular septum was intact Fallot's tetralogy could be excluded. In the latter case a reversed interatrial shunt was assumed to be present though often difficult to prove.[28] A complete analysis of the findings in each case is presented elsewhere.[6] Necropsy confirmation of the diagnosis was obtained in seven cases.

In addition to full clinical examination, special attention was devoted to auscultation. All cases of pulmonary or infundibular stenosis had a systolic murmur (grade 2 to 5[7]) usually maximal in the second left intercostal space but occasionally in the third and fourth left spaces. Special care was taken

at the site of maximal intensity of the murmur to determine whether the murmur was loudest in early, mid or late systole. Even more important, the relation of the end of the murmur to the second sound was observed. The presence or absence of splitting of the second sound was noted. Lastly the first heart sound and diastole were studied for any abnormality.

The Sanborn Stetho-Cardiette was used to obtain phonocardiograms in each case. Logarithmic (high frequency) sound tracings, which give an accurate graphic representation of human hearing[8-10] were recorded synchronously with a suitable electrocardiographic lead, carotid or jugular pulse tracing. The sound recordings were taken in succession from the mitral area (MA), fourth left intercostal space just to the left of the sternum (4LS), the third left space (3LS), pulmonary area (PA) and aortic area (AA). The amplification chosen was purely qualitative, designed to give the best record for a particular purpose. Thus to record a very soft sound greater amplification was used. The carotid and jugular tracings were obtained by placing a crystal microphone directly on the neck, thus avoiding delay from air conduction.

The components of split first and split second sounds were identified by determining their respective relationship to the onset and nadir of the dicrotic notch of a synchronously recorded right carotid pulse tracing. Tracings taken at high speed (75 mm. per second) were essential for accurate study. Since the dicrotic notch is produced by aortic valve closure, it can be used to identify the components of a widely split second sound [11-13] (figs. 4, 6 to 8). Thus the onset of the component due to aortic valve closure, precedes the nadir of the notch by a short interval (average 0.03 second), due to the delay in pulse wave transmission from the aortic valve to the carotid artery. It was assumed that the component occurring after the dicrotic notch could only be due to pulmonary valve closure. In very wide splitting of the second heart sound as encountered in severe pulmonary stenosis, the soft pulmonary component may be mistaken for a third heart sound. The relation of this sound to the summit of the "v" wave in the jugular phlebogram was used to exclude a third heart sound arising from the right ventricle (figs. 4 and 6). The fact that the soft sound just preceded the "v" wave indicated that it was produced just before opening of the tricuspid valve, at the time of pulmonary valve closure. The occurrence of this sound only in the pulmonary area and third left space is in keeping with a soft pulmonary second sound and unlike a third sound arising in the left ventricle, which is best heard at the apex or just internal to it.

Synchronous carotid tracings gave a time relation between the first sound, added early systolic sounds and the opening of the aortic valve (figs. 4, 10 and 11).[11-13] Delay in pulse wave transmission from aortic valve to carotid artery was assumed to be given by the time interval from the onset of aortic component of the second sound to the nadir of the dicrotic notch. This interval averaged, as in a previous study,[12] 0.03 second.

Results

Auscultatory and phonocardiographic findings are shown in tables 1 and 2 and figures 1 and 2.

Discussion

The Second Heart Sound

The second sound is produced by closure of the aortic and pulmonary valves and asynchronous closure of these valves results in splitting of the second sound. Splitting in the pulmonary area is an almost invariable finding in healthy children and young adults. The degree of splitting is greatly influenced by respiration; splitting is widest at the end of inspiration and narrows or disappears during expiration. By means of synchronous phonocardiograms from the mitral, aortic and pulmonary areas, Leatham and Towers[14] showed that the pulmonary valve normally closes after the aortic valve. This had also been shown by Wolferth and Margolies in their studies of bundle branch block, using aortic kymograms and carotid artery tracings.[11] Splitting is best heard in the second and third left intercostal spaces but not in the mitral and aortic areas because the normal pulmonary component is not usually conducted to these areas.[15, 10] Increase in the width of splitting on inspiration is due to delay of the pulmonary component. The delayed closure of the pulmonary valve induced by inspiration has been attributed not only to the fall in pulmonary artery diastolic pressure, but also to prolongation of right ventricular systole from increased filling.[10]

It has become important during auscultation to note both the degree of splitting and the intensity of the two components of the second sound in the pulmonary area. Splitting may be normal (grade 1 and 2) or abnormally wide (grade 3 and 4).[16] A well known example of abnormal splitting is that often found in right bundle branch block presumably due to delayed activation of the right ventricle. Comparison of the intensity of each component also provides important information. Thus in pulmonary hypertension the pulmonary element is accentuated and is audible over a wide area even as far as the apex.

We have paid special attention to the presence or absence of splitting, and to the degree of reduction of intensity of the pulmonary component in cases of pure pulmonary stenosis of differing severity and in cases of Fallot's tetralogy. Pulmonary valvular stenosis and infundibular stenosis, unlike aortic stenosis,

TABLE 1.—*Auscultatory Findings in Six Patients with Severe Pulmonary Stenosis with Intact Ventricular Septum and Right-to-Left Interatrial Shunt*

No.	Case, age, sex	Central cyanosis (1–4)	Disability (1–4)	Auscultation								Phonocardiogram	Site of stenosis	Proof
				Systolic murmur (at site of max. intensity)			2nd sound (at site of max. intensity of SM.)		1st sound	Atrial sound	Diast. murmur			
				Site of max. intensity	Grade (1–6)	Relation to 2nd sound	Single or split	Intensity						
1	E. B., 49, F	2	3	PA	4	Long SM. Stops before soft P_2. A_2 not heard.	Single	Very soft	Loud and click-like on exp. only. Max. in PA.	Loud on insp.	0	A_2 buried in prolonged SM which stops before soft P_2. Width of split about 0.13 sec. Loud first sound on expir.; loud auric. sound on inspir.	Valvular	Necropsy
2	S. J., 9, F	1	1	4LS	5	Long SM. A_2 & P_2 inaudible.	0	0	N	0	0	A_2 buried in prolonged SM. No P_2 recorded. Normal A_2 at MA & AA.	Valvular	Cath. Angio. Valvotomy
3	J. F., 36, F	3	2	PA	4	Long SM. Stops before soft P_2. A_2 not heard.	Single	Very soft	N	Loud on insp.	Presystolic (Max. in PA)	A_2 buried in prolonged SM, which stops before soft P_2. Width of splitting about 0.14 sec. Loud auric. sound and presyst. murmur	Valvular	Cath. Sel. angio (RV).
4	N. S., 22, F	3	2	3LS	3	Long SM. A_2 & P_2 inaudible.	0	0	N	0	0	PCG taken after valvotomy. Prolonged SM extends beyond A_2 but does not obscure it. No P_2.	Valvular	Cath. Angio. Valvotomy
5	P. P., 42, M	1	2	PA	4	Long SM. Stops before soft P_2. A_2 just audible.	Split (Very wide.)	A_2 N P_2 very soft	Loud and click-like on exp. only. Max. 3LS.	Loud on insp.	0	A_2 buried by prolonged SM, which stops before soft P_2. Width of split ca. 0.11 sec. Loud first sound on exp., loud auric. sound on insp.	Valvular	Cath. Angio.
6	S. D., 10, M	1	1	PA	5	Long SM. A_2 & P_2 inaudible.	0	0	Loud and sharp.	0	0	A_2 buried by prolonged SM which stops before soft P_2. Width of split ca. 0.11 sec.	Valvular	Cath. Sel. angio (RV.)

A_2 = Aortic component of second sound. P_2 = pulmonary component of second sound. Sel. angio (RV.) = selective angiocardiogram from right ventricle.

result in a fall in pressure distal to the obstruction and in consequence the second or pulmonary component of the second sound becomes soft or inaudible depending upon the degree of stenosis. Furthermore, the low pulmonary diastolic pressure and probable prolongation of the right ventricular systole results in delayed closure of the pulmonary valve so that *wide splitting* of the second sound is heard or recorded provided the pulmonary component is loud enough.

The Second Sound in Severe Pulmonary Stenosis with Closed Ventricular Septum. It is easier to understand the findings in severe pulmonary stenosis if one first considers the changes that occur in mild pulmonary stenosis. In most cases of mild pulmonary stenosis, as defined by Abrahams and Wood,[16] we heard and recorded a normal to widely split second sound with a normal to soft pulmonary component (fig. 3). The pulmonary systolic murmur in all cases filled systole extending up to the first or aortic component of the split second sound. Even in cases of moderate pulmonary stenosis it was often possible to hear wide splitting of the second sound but the pulmonary component was always abnormally soft, thus confirming the previous observations of Leatham.[10] An exaggeration of these findings might be anticipated in severe pulmonary valvular stenosis.

In *severe* pulmonary stenosis clinical analysis of the altered second sound is difficult. In three of the 6 cases the harsh prolonged pulmonary systolic murmur stopped before an extremely soft sound, but in the remaining three no pulmonary component could be heard. In one case only (case 5, P. P.) was very wide splitting (grade 4) appreciated by the ear. In this case the aortic component was not completely obscured by the murmur. The phonocardiogram with synchronous carotid and jugular tracings were essential in analysing these changes. In each case the systolic murmur in the pulmonary area was so prolonged that it had extended beyond the first or aortic component of a widely split second sound (figs. 4 and 8). In fact the aortic sound was completely buried in the murmur in all except one case. The buried sound could be identified by the dicrotic notch of the carotid tracing and also by sound tracings taken at the apex or fourth left space where a normal aortic sound was less obscured by the systolic murmur (fig. 4). The systolic murmur ended before a very soft pulmonary second sound which was recorded in four out of six cases, thus proving that *very wide* splitting was in fact present in severe pulmonary stenosis. In the remaining two cases the second sound was presumably so soft that even considerable amplification failed to reveal its presence.

Thus in severe pulmonary stenosis with intact septum, although the phonocardiogram demonstrates very wide splitting of the second sound and may therefore be useful as a special test, clinical auscultation at the site of maximal intensity merely reveals a harsh prolonged systolic murmur which may be followed by a very soft pulmonary second sound. However, auscultation in the mitral area and fourth left space where the murmur is less intense reveals an aortic second sound of normal intensity.

The Second Sound in Fallot's Tetralogy. In Fallot's tetralogy, where the severity of the stenosis is of an order comparable to severe pulmonary stenosis with intact septum, a similar alteration of the second sound might be anticipated. This is, in fact, not the case. In Fallot's tetralogy the second sound is often abnormally loud and thus usually palpable (table 2). This may be due to the fact that the aortic valve is brought closer to the anterior chest wall by the dextroposition of the aortic root. Furthermore, the systolic murmur finishes or diminishes markedly before the aortic second sound (vide infra) thereby contributing to the striking clarity of the second sound in Fallot's tetralogy. Phonocardiograms confirmed these clinical findings in all cases (figs. 2 and 5). Comparison of figure 4 with figure 5 shows how the aortic second sound is obscured by the prolonged systolic murmur in severe pulmonary stenosis with intact septum whereas in Fallot's tetralogy the loud aortic second sound stands well to the right of a shorter pulmonary systolic murmur.

The problem of the pulmonary second sound in Fallot's tetralogy is of considerable academic

TABLE 2.—*Auscultatory Findings in 18 Patients with Fallot's Tetralogy*

No.	Case, age, sex	Central cyanosis (1–4)	Disability (1–4)	Auscultation									Phonocardiogram	Site of stenosis	Proof
				Systolic murmur (at site of max. intensity)			2nd sound (at site of max. intensity of SM.)		1st sound	Atrial sound	Diast. murmur				
				Site of max. intensity	Grade (1–6)	Relation to 2nd sound	Single or split	Intensity							
7	H. J., 16, F	3	2	PA	3	Short SM. Stops before A_2.	Single	Loud (palpable)	N	0	0		SM max. before midsystole. Stops before loud A_2. No P_2.	Infundib.	Necropsy
8	W. K., 9, F	3	3	PA	4	Short SM. Stops well before A_2.	Single	Loud (palpable)	N	0	0		SM max. by midsystole. Stops well before loud A_2. Very soft P_2. Width of split 0.09 sec.	Valvular	Cath. Angio.
9	E. W., 19, M	3	1	PA	3	SM stops before A_2.	Single	Loud (palpable)	N	0	0		SM stops just before loud A_2. No P_2.	Infundib.	Necropsy
10	C. G., 8, M	1	3	PA	5	SM stops well before A_2.	Single (pre-op) Split (post-op)	Loud (palpable) P_2 v. soft post-op.	N	0	0		SM max. by midsystole. Stops before loud A_2. No P_2. Post-Op: Soft P_2. Width of split 0.08 sec.	Infundib.	Cath. Sel. Angio. (RV) Blalock-Taussig op.
11	R. P., 27, F	2	1	3LS	4	SM stops before A_2.	Single	Loud (palpable)	N	0	0		SM max. before midsystole. Stops just before loud A_2. No P_2.	Infundib.	Cath. Angio.
12	E. K. 10, M	2 (Preop 3)	3 (Preop 4)	3LS	2	Short SM. Stops well before A_2.	Single	Loud (palpable)	Aortic early systolic sound at all areas.	0	0		Short SM. Stops long before loud A_2 No P_2. Split 1st sound plus aortic early systolic sound.	Infundib. (Severe)	Cath. Blalock-Taussig op.
13	V. B., 5, M	4	4	3LS	2	Very short early SM. Stops long before A_2.	Single	Loud (palpable)	Aortic early systolic sound at all areas.	0	0		Very short early SM. Loud A_2. No P_2. Split 1st sound plus aortic early systolic sound.	Infundib. (Extreme)	Necropsy
14	L. E., 29, F	2	2	4LS	4	SM stops before A_2.	Single	Loud (palpable)	N	0	0		SM max. by midsystole. Stops before loud A_2. No P_2.	Infundib.	Cath. Angio. Blalock-Taussig op.

15	L. K., 6, M	4	4	3LS	2	Short SM stops well before A_2.	Single	Loud	Aortic early systolic sound loud at all areas.	0	0	Short SM after aortic early systolic sound. Stops before loud A_2. No P_2.	Infundib. plus Valvular (extreme)	Necropsy
16	C. S., 14, M	3	2	4LS	5	SM stops before A_2.	Single	Loud (palpable)	N	0	0	SM max. in midsystole. Stops just before A_2. No P_2.	Infundib. plus Valvular	Cath. Sel. Angio (RV)
17	S. P., 17, M	2	1	PA	4	SM stops just before A_2.	Split	A_2 loud P_2 soft	Loud	0	0	SM max. in midsystole. Stops at loud A_2. P_2 recorded. Width of split 0.08 sec.	Valvular	Cath.
18	A. H., 5, M	1	3	PA	4	SM stops well before A_2.	Single	Loud (palpable)	N	0	0	SM max. before midsystole. Ends before loud A_2. No P_2.	Infundib.	Cath.
19	N. J., 18, F	4	3	PA	4	SM stops well before A_2.	Single	Loud (palpable)	N	0	0	SM max. before midsystole. Ends well before A_2. No P_2.	Infundib.	Angio.
20	R. B., 12, M	2	1	3LS	4	SM stops before A_2.	Single	Loud (palpable)	N	0	0	SM max. by midsystole. Stops before loud A_2. No P_2.	Infundib. plus Valvular	Cath. Sel. Angio (RV).
21	L. K., 5, M	1	1	3LS	5	SM longer than usual but stops before A_2.	Single	Loud	N	0	0	SM Max. in midsystole. Stops just before loud A_2. Very soft P_2. Width of split 0.08 sec.	Infundib. plus Valvular	Cath. Angio.
22	R. M., 7, F	4	3	3LS	1	SM very short and early.	Single	Loud (palpable)	Aortic early systolic sound at all areas.	0	0	Very short early SM. Stops before midsystole. Aortic early systolic sound.	Valvular (extreme)	Necropsy
23	J. V., 35, F	1	1	PA	4	SM stops before A_2.	Single	Loud (palpable)	Loud	0	0	SM max. by midsystole. Stops just before loud A_2. No P_2.	Infundib.	Cath. Sel. Angio (RV).
24	M. F., 7, F	4	3	PA	4	SM stops well before A_2.	Single	Loud (palpable)	N	0	0	SM max. before midsystole. Stops well before loud A_2. No P_2. Variable mid-systolic click.	Infundib. (severe)	Necropsy

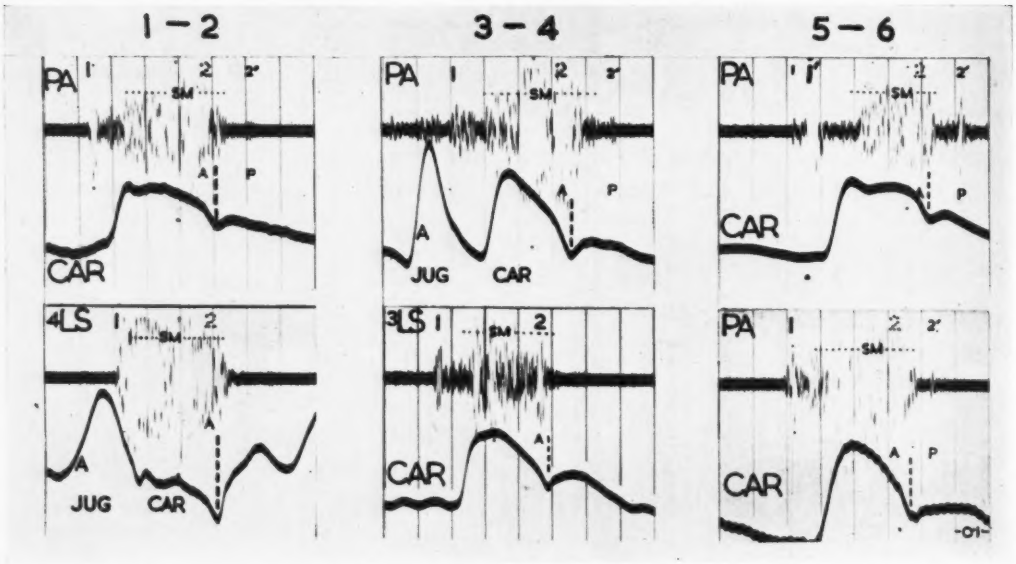

FIG. 1. *Six cases of Severe Pulmonary Stenosis with Intact Ventricular Septum and Right-to-Left Interatrial Shunt.* In all the phonocardiograms were taken at the site of maximal intensity of the murmurs. In each case the systolic murmur (SM) is intense and so prolonged that it extends beyond and drowns the normal aortic component (A) of the very widely split second sound (2,2′). It stops before the delayed diminutive pulmonary component (P) when recorded. With the exception of case 4, which was recorded after a partially successful pulmonary valvotomy, the approximate position of the buried aortic component is indicated by the dicrotic notch of the synchronously recorded carotid pulse. Black dots have been used to indicate the limits of the sound vibrations in this and subsequent figures.

interest. It is generally stated that a pure single second sound occurs in Fallot's tetralogy. While this is usually true our observations prove that in some cases the pulmonary second sound follows the aortic second sound and we believe that splitting of the second sound in Fallot's tetralogy would be elicited more often were it not for the fact that the pulmonary valve closure is so quiet. In one remarkable case (case 17, S. P.) of proven Fallot's tetralogy, wide splitting of the second heart sound was easily detected clinically (fig. 6) and gave rise to considerable diagnostic difficulties. The unusually high pulmonary artery pressure found in this case seemed the best explanation of the audible pulmonary second sound. In case 10 (C. G.) careful auscultation two months after a successful Blalock-Taussig operation revealed definite splitting of the second heart sound whereas prior to operation only a single second sound was heard and recorded (fig. 7). The appearance of the soft pulmonary second sound after the operation suggested that the pulmonary artery pressure had risen above a critical level necessary for production of audible valve closure. In two further cases (case 8, W. K., and case 21, L. K.) a definite diminutive pulmonary second sound was recorded but not heard. This evidence suggests that the usual single second sound in Fallot's tetralogy is not due to synchronous closure of the aortic and pulmonary valves. It is, in fact, due to aortic valve closure alone, which is followed by pulmonary valve closure, presumably inaudible because of the low pulmonary diastolic pressure.

Although the series is small, the width of splitting in Fallot's tetralogy appears to be considerably less than that in severe pulmonary stenosis with intact septum (figs. 4, 6, 7 and 8). In both conditions there is a low pulmonary diastolic pressure which is a

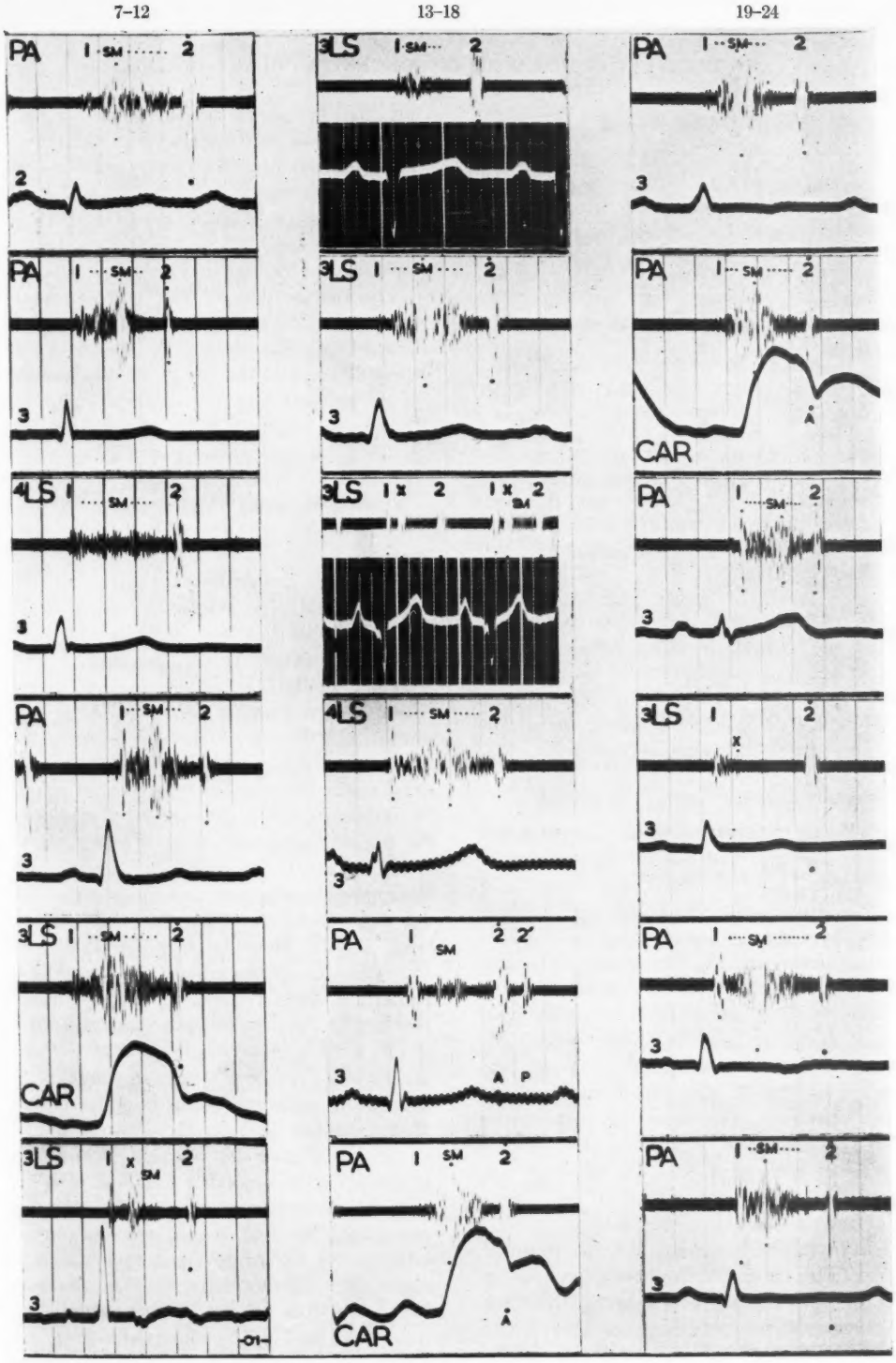

FIG. 2. *Eighteen Cases of Fallot's Tetralogy.* In all cases the phonocardiograms were taken at the site of maximal intensity of the murmur. In each case the murmur commences soon after the first sound, reaches maximal intensity by midsystole, and then diminishes markedly, usually ending before the single, loud aortic component of the second sound which is not in any way obscured by the murmur. In the four most severe cases (cases 12, 13, 15 and 22) the systolic murmur was soft, early and short.

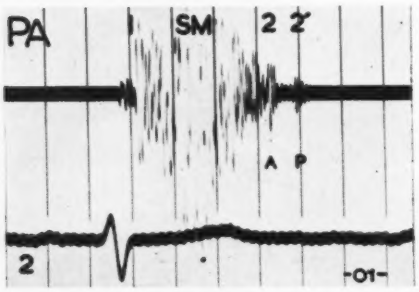

FIG. 3. Synchronous phonocardiogram (PCG) at the pulmonary area (PA) and lead II (75 mm./sec.), from a case of *mild* pulmonary valve stenosis with intact septum (RVP 30/0; PAP 10/4 mm. Hg). The loud systolic murmur (SM) fills systole, extending up to, but not obscuring, the first or aortic component (A) of the well split second sound. The second or pulmonary component (P) is moderately reduced in intensity.

important common factor in the production of the split sound. It is suggested that the greater delay of the pulmonary component in severe pulmonary stenosis with intact septum is due to the additional factor of prolongation of right ventricular systole (vide infra).

The Systolic Murmur

In all cases studied a systolic murmur was present. The murmur was usually harsh and loud (grade 3 to 5[7]) in which case its intensity was of no help in differentiating the two conditions. However, in four cases of Fallot's tetralogy (cases 12, 13, 15 and 22), all severe, the systolic murmur was soft (grade 1 or 2). On this basis alone Fallot's tetralogy was favored as in all cases of severe pulmonary stenosis with intact ventricular septum the murmur was loud.* The site of maximal intensity, however, was of no real help in the differential diagnosis. Where the stenosis was valvular in both conditions, the murmur was maximal at the second and third left intercostal spaces (with the exception of case 2, S. J.). In infundibular stenosis the murmur was as often maximal in the second as in third and fourth intercostal spaces. A murmur maximal in the fourth space favored infundibular stenosis and hence Fallot's tetralogy because infundibular stenosis occurs so much more commonly in this condition. However, in one case of valvular stenosis with intact ventricular septum (S. J.), the murmur was maximal in the fourth intercostal space.

Previous studies of the systolic murmur have failed to reveal any characteristic distinguishing feature.[4, 10, 16-25] We agree that the loudness and the site of maximal intensity of the murmur is usually of no real help in the differential diagnosis of Fallot's tetralogy from severe pulmonary stenosis with intact septum. However, we have found that there is a striking difference in the two murmurs, if attention is directed to the duration of the systolic murmur in relation to the second sound and to the position in systole of maximal intensity. Our findings have led us to believe that an accurate diagnosis can be made by careful bedside auscultation.

The Systolic Murmur in Severe Pulmonary Stenosis with Intact Ventricular Septum. Auscultation *at the site of maximal intensity* of the murmur reveals a prolonged systolic murmur. The aortic component of the second sound is rarely heard, being drowned by the crescendo of the murmur (figs. 1, 4, 8). The murmur stops before the delayed diminutive pulmonary component which may occasionally be heard by very careful auscultation in the pulmonary area. In the mitral area where the systolic murmur is much less intense, the aortic second sound, of normal intensity, is not drowned and is therefore usually clearly audible (fig. 4).

The Systolic Murmur in Fallot's Tetralogy. In Fallot's tetralogy the behaviour of the pulmonary systolic murmur is quite different. However loud or soft, the systolic murmur *at the site of maximal intensity*, is much less prolonged than in severe pulmonary stenosis with intact ventricular septum. It commences soon after the first sound, reaches maximal intensity by mid-systole and then diminishes markedly, usually ending before the single loud aortic component of the second sound (figs. 2, 5, 6, 7). The phonocardiogram may record small rapidly diminishing vibrations right up to the second sound, but these are

*We have since encountered one case of unusually severe pulmonary stenosis in heart failure in whom the systolic murmur was grade 2 only.

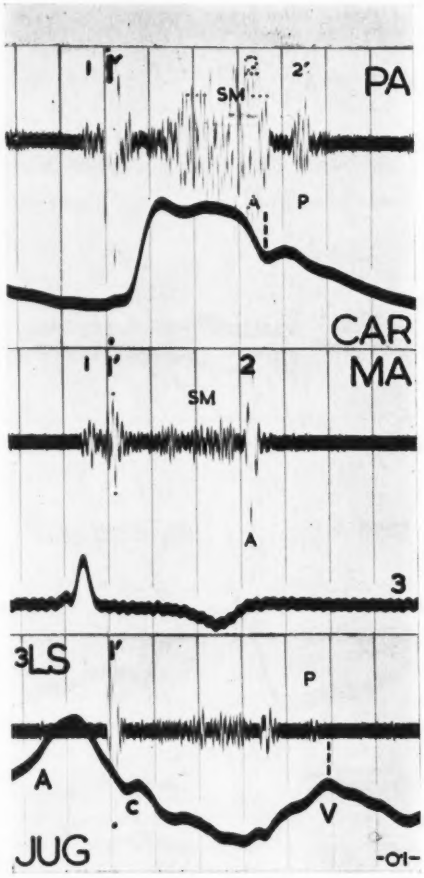

FIG. 4. *Case 5 (P. P.) Severe Pulmonary Stenosis with Intact Septum.* The systolic murmur at the site of maximal intensity (PA) is so prolonged that it extends beyond the first or aortic component (A) of the very widely split second sound (2,2'). The aortic sound is, in fact, completely buried in the murmur. The buried sound can be identified by the dicrotic notch of the carotid tracing (CAR) and by the PCG taken at the mitral area (MA) where the normal aortic sound (A) is not obscured by the systolic murmur. The systolic murmur ends before the soft pulmonary component (P). The latter is identified by the fact that it just precedes the "V" wave of the jugular venous tracing (JUG) indicating that it is produced just before opening of the tricuspid valve, at the time of pulmonary valve closure. The tracing also records the extremely intense "second component" (1') of the first sound maximal in the PA commencing 0.01 second before the onset of ejection into the aorta (a delay of 0.03 second in pulse wave transmission from the aortic valve to the carotid artery has been assumed). As the heart rate was identical, the tracings as mounted, here and elsewhere, are virtually synchronous.

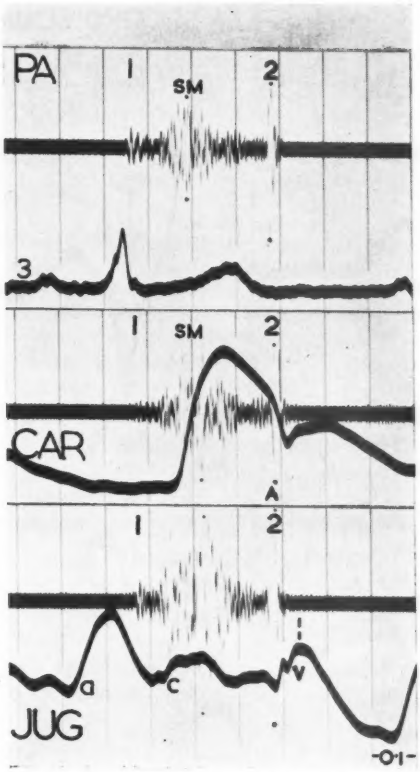

FIG. 5. *Case 20 (R. B.). Fallot's Tetralogy.* The systolic murmur at the site of maximal intensity (PA) commences soon after the first sound (1), reaches maximal intensity by mid-systole and diminishes markedly ending before the loud aortic component of the single second sound (A), which is identified by the dicrotic notch of the carotid tracing. Pulmonary valve closure is not recorded but it must occur before the summit of the "V" wave (i.e. within 0.08 second after the onset of the aortic second sound).

not detected by the ear, the murmur appearing to end well before the loud second sound.

As far as we are aware this difference in the behavior of the pulmonary systolic murmur in the two conditions has not been hitherto described.

COMMENT

The striking difference in the duration of the systolic murmur can probably be related

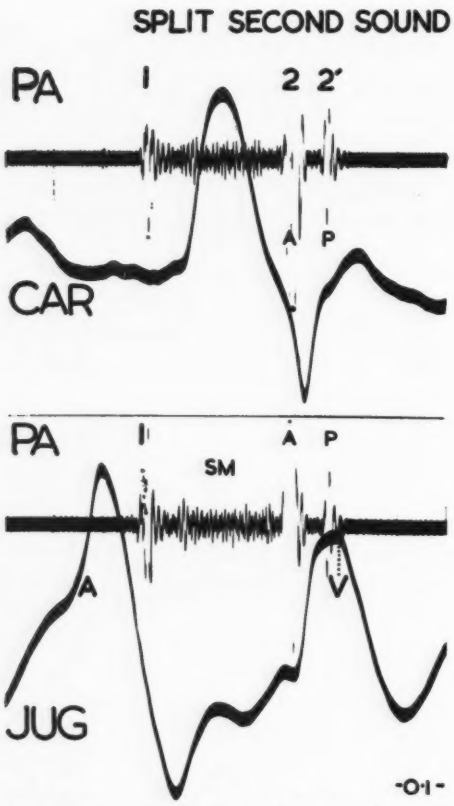

FIG. 6. *Case 17 (S. P.) Fallot's Tetralogy.* The systolic murmur commences soon after the first sound and ends before the loud aortic component (A) of the second sound which is identified by the dicrotic notch of the carotid tracing The unusually loud pulmonary component (P) is identified by the fact that it just precedes the "V" wave of the jugular venous tracing. The width of splitting measures 0.08 second as compared with 0.11 second in figure 4 and ca. 0.14 second in figure 8.

FIG. 7. *Case 10 (C. G.) Fallot's Tetralogy.* (a) The systolic murmur reaches maximal intensity by midsystole and diminishes markedly before the loud aortic component of the single second sound. (b) Two months after a Blalock-Taussig operation the pulmonary component (P) of the second sound became just audible giving rise to splitting of the second sound (2,2'), measuring 0.08 second.

to the fundamentally different dynamics of the two conditions.

In severe pulmonary stenosis with intact ventricular septum the right ventricle alone has to develop great pressure to effect adequate blood flow across the stenotic valve. Thus the systolic pressure in the right ventricle often exceeds the aortic and left ventricular systolic pressures, especially after effort.[25-28, 16, 40, 6] The giant "a" wave in the venous pulse is indicative of the right atrial hypertrophy which augments filling of the right ventricle and assists it in generating such high pressures.[30, 16, 40] A considerable difference in the amplitude and duration of the pressure curves in the right and left ventricles must occur. We have shown that the second sound is widely split due to marked delay of the very soft pulmonary component. The delayed closure of the pulmonary valve is due not only to the low pulmonary diastolic pressure, but also to prolongation of the ejection phase of right ventricular systole as compared with that of the left ventricle. Flow will continue across the stenotic pulmonary valve as long as a pressure gradient exists between the right

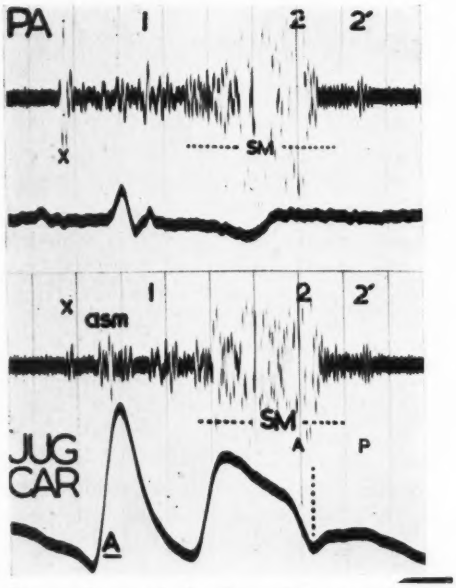

FIG. 8. *Case 3 (J. F.) Severe Pulmonary Stenosis with Intact Septum.* The prolonged systolic murmur reaches a late crescendo completely obscuring the aortic component (A) of the second sound, as identified by the dicrotic notch of the carotid tracing. It ends before the soft pulmonary component (P) of the very widely split (ca. 0.14 second) second sound (2,2'). The loud atrial sound (X) is followed by a murmur (asm). This presystolic murmur occurs after the onset of right atrial contraction which is unusually powerful as revealed by the giant "a" wave (A).

ventricle and the pulmonary artery. Thus when the aortic valve closes at the end of the normal or reduced left ventricular systole active flow still continues across the pulmonary valve. Since the intensity of the systolic murmur is probably proportional to the speed and volume of flow, other factors such as degree of stenosis and viscosity being equal, it is not surprising to find the pulmonary systolic murmur continuing beyond the aortic second sound (diagram I).

In Fallot's tetralogy, unlike severe pulmonary stenosis with intact ventricular septum, the ventricular septal defect and the over-riding aorta both act as a safety valve to the right ventricle; no matter how severe the pulmonary or infundibular stenosis, the right ventricular systolic pressure can never significantly exceed that in the aorta and left

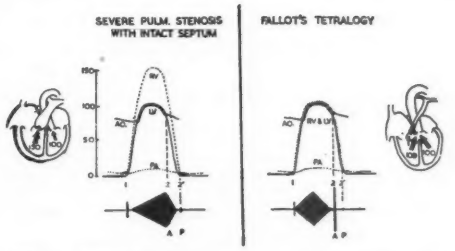

Diagram I: The diagram attempts to explain the dynamic basis for the striking difference in the duration of the systolic murmur in relation to the aortic second sound (2, A) and greater width of splitting in severe pulmonary stenosis with intact ventricular septum. See text for details.

ventricle.[16, 25, 27-29] Thus clinical evidence of right ventricular and right atrial hypertrophy is much less. This is shown by the absence of a giant "a" wave in the venous pulse, the slight lift over the right ventricle and the absence of marked right ventricular enlargement radiologically. In Fallot's tetralogy the right and left ventricles virtually function as a single ventricle from which blood is discharged into two competing orifices, namely the aortic with normal systemic peripheral resistance* and a stenotic pulmonary valve or infundibulum with a much higher resistance. The ventricular pressure curve in both ventricles is conditioned by the lesser resistance offered by the aorta and hence adaptation to the severe pulmonary stenosis is much less effective than in pulmonary stenosis with an intact septum. Thus effective systole cannot be more prolonged in the right ventricle than the left because by the time the aortic valves close the ventricles have virtually discharged their contents. This is well illustrated by angiocardiography which reveals rapid discharge of diodone from the right ventricle into the aorta in Fallot's tetralogy contrasting sharply with the delayed emptying of the right ventricle seen in severe pulmonary stenosis with intact septum.[31, 32, 26, 41] Maximal flow across the stenotic valve or chamber occurs early in systole at the time of

* This has not been measured by us but the absence of hypertension in our cases of Fallot's tetralogy at least indicates a normal systemic peripheral resistance.

maximal flow into the aorta; during the phase of reduced ejection from the ventricles into the aorta, flow into the pulmonary artery is likewise reduced. By the time the aortic valve closes flow into the pulmonary artery has virtually ceased being entirely dependent on the rapidly diminishing pressure gradient between the right ventricle and pulmonary artery and the little available residual blood.

It is therefore not surprising that the pulmonary systolic murmur* in Fallot's tetralogy attains maximal loudness by mid-systole and then diminishes rapidly, usually ending before the aortic second sound. Variation in the intensity and duration of the murmur does, however, occur. In our four most disabled patients (cases 12, 13, 15 and 22, in three of whom extreme stenosis was proven at necropsy) the murmur was soft and short reaching a crescendo well before midsystole and ending long before the aortic second sound (figs. 2, 12 and 10). A short murmur thus appears to indicate severe stenosis. This inference is not unreasonable for the severer the stenosis the less the flow across the pulmonary valve. Unlike pulmonary stenosis with intact septum, the systemic peripheral resistance and not the pulmonary stenosis determines the level of the right ventricular systolic pressure. This is grossly inadequate in extreme pulmonary stenosis and thus flow sufficient to produce a murmur is limited to the early ejection phase of the right ventricle. In milder cases of Fallot's tetralogy the murmur appears to be longer (fig. 12) but we have not yet encountered any case in which the murmur obscured the second sound.†

Auscultatory Observations of Lesser Diagnostic Value

Diastolic Murmurs. No case had pulmonary or aortic incompetence. In one case of severe pulmonary stenosis with intact ventricular septum (case 3, J. F.), a presystolic murmur was well heard in the second, third and fourth intercostal spaces, being loudest in the pulmonary area. It was not heard at the apex. The murmur was preceded by a loud atrial sound also best heard at the pulmonary area (fig. 8). The murmur occurred after the onset of right atrial contraction which was unusually powerful as revealed by the giant "a" wave (fig. 8). Cardiac catheterisation showed a right atrial systolic pressure of considerable magnitude transmitted into the left atrial and pulmonary veins as reported elsewhere.[6] Abrahams and Wood[16] have encountered in severe pulmonary stenosis a similar presystolic murmur which they attributed to flow across a patent foramen ovale shown at necropsy. In our case flow across the pulmonary valve produced by the powerful right atrial contraction may be an alternative explanation.

The Atrial Sound. In three cases of severe pulmonary stenosis with intact ventricular septum (cases 1, 3 and 5), a singularly loud

* We are in agreement with the generally held view that the ventricular septal defect plays little or no part in the production of the systolic murmur in Fallot's tetralogy. Marked unidirectional flow from one ventricle to the other as found in ventricular septal defect with normal aortic root and normal pulmonary vascular resistance does not occur in Fallot's tetralogy because the pressures in both ventricles are of the same order and the overriding aorta provides a common exit. Moreover, in other conditions associated with a ventricular septal defect and similar ventricular dynamics (Eisenmenger's complex, truncus and pseudotruncus arteriosus), there is often no systolic murmur (fig. 11), and, if present, the murmur is short and does not resemble Roger's murmur.

† Unusual prolongation of the systolic murmur in Fallot's tetralogy may occasionally occur. The second sound, however, is still not obscured by the murmur. In our only case of proven Fallot's tetralogy where this occurred, coarctation of the aorta was also present, causing a systemic blood pressure of 170/80 mm. Hg. It is probable that the unusually high right ventricular systolic pressure conditioned by the high aortic resistance permitted vigorous flow to continue through the stenosed pulmonary valve for a longer duration than the usual case of Fallot's tetralogy. This is supported by the fact that the patient's cyanosis had disappeared clinically during observation over several years, and his effort tolerance had increased. Furthermore, the pulmonary artery pressure was unusually high and the second sound was widely split with a very soft but audible pulmonary component. Being complicated by coarctation the case has not been included in this series but is discussed elsewhere.[6]

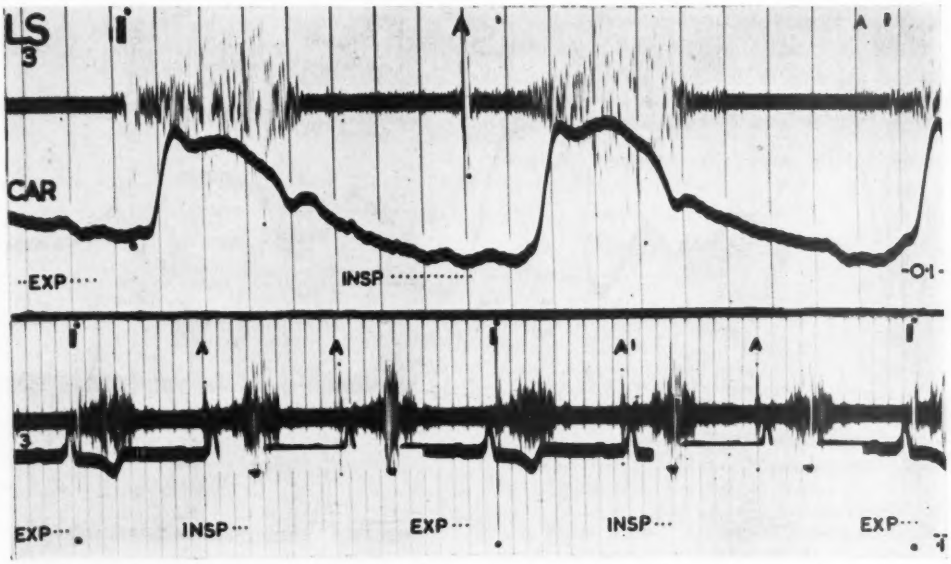

FIG. 9. *Case 1 (E. B.). Severe Pulmonary Stenosis with Intact Septum.* (a) Synchronous phonocardiogram at 3 LS and carotid tracing at 75 mm./sec. (b) synchronous phonocardiogram at 3 LS and lead III at 25 mm./sec.

An extremely loud *first* sound appears suddenly during expiration only to disappear completely during inspiration (INSP.). It occurs just after the *first* sound and before the onset of the carotid pulse. The marked effect of respiration on the atrial (A) is recorded, being loud during inspiration and absent during expiration. The characteristic systolic murmur of pulmonary stenosis with intact septum is also shown.

auricular sound was heard and recorded in the second, third and fourth intercostal spaces but not at the apex (figs. 8 and 9). The intensity was markedly influenced by the phase of respiration, being loud during inspiration and soft during expiration (fig. 9). This sound was attributed to vibrations occurring in the right ventricle or pulmonary valve produced by the powerful atrial systolic filling wave.

In no case of Fallot's tetralogy was an atrial sound heard. This is in keeping with the concept already discussed that the right ventricle and right auricle in Fallot's tetralogy are under far less stress than in severe pulmonary stenosis with intact ventricular septum. It is concluded that an audible atrial sound favours the diagnosis of severe pulmonary stenosis with intact septum.

The First Heart Sound. Several points of interest emerged from the study of the first sound which require further investigation and may prove to be of additional diagnostic value.

In Fallot's tetralogy the first sound was usually normal, being either single or closely split. In four cases it was apparently "widely split". The second component, however, was not attributed to the second component of a physiologically split first sound but to an aortic early systolic sound[12] because of the wide transmission to all areas including the aortic area and the marked degree of splitting. Furthermore, the phonocardiogram proved the separate identity of this added sound by showing normal splitting of the first sound preceding the aortic sound (fig. 10). Moreover, this sound occurred about 0.04 second after ejection into the aorta, a delay of 0.03 second in pulse wave transmission from aortic valve to carotid artery being assumed. The aorta is dextroposed and nearer the chest wall than normal. It is dilated and receives a greater

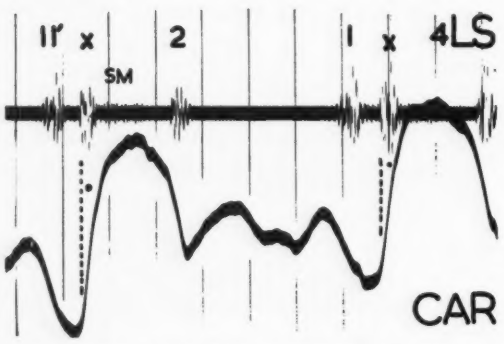

FIG. 10. *The Aortic Early Systolic Sound in Severe Fallot's Tetralogy.* (*Case 12, E. K.*) There is normal splitting of the first sound (1,1') followed by a loud aortic early systolic sound (X). This sound occurred about 0.04 second after the onset of rise of pressure in the aorta (a delay of 0.03 second in pulse wave transmission from aortic valve to the carotid artery has been assumed). The added ejection sound was transmitted widely to all areas including the aortic area. The characteristic systolic murmur of Fallot's tetralogy although soft is also shown.

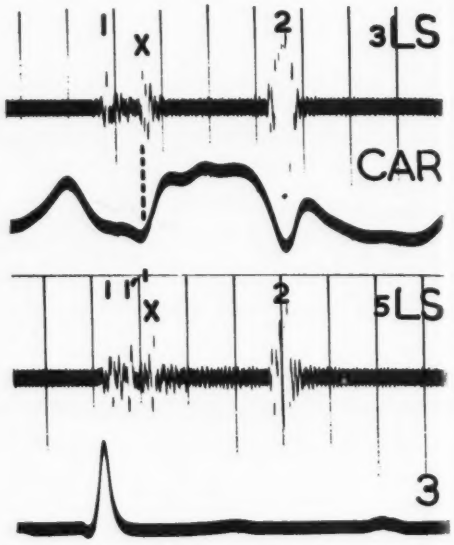

FIG. 11. *The Aortic Early Systolic Sound in Pulmonary Atresia.* There is normal splitting of the first sound (1,1') at 5 LS followed by a loud early systolic sound (X). This sound occurred about 0.03 second after the onset of ejection into the aorta. As this case had pulmonary atresia the ejection sound could only be "aortic". It had the same features as the ejection sound (X) shown in figure 10.

volume of blood than normal, being the main exit of blood from both ventricles. These factors may be responsible for this audible ejection sound. The presence of this sound appears to be an indication of the severity of the lesion. The more severe the pulmonary stenosis the greater the volume of blood ejected into the aorta, and hence the larger the aorta. This combination favours the production of an audible ejection sound. This sound was only present in our four most disabled cases (cases 12, 13, 15 and 22). Furthermore, in two cases of pulmonary atresia, where the output of both ventricles was discharged into a single dilated "pseudotruncus arteriosus", a striking aortic systolic sound was heard (fig. 11). Although the aortic early systolic sound has been described in a variety of conditions affecting the aorta and aortic valves,[33, 34, 12] its occurrence in Fallot's tetralogy is much less well known[35, 36] and in pulmonary atresia it has not been described before.

In severe pulmonary stenosis with intact septum the first sound was usually normal. However, in two cases of this series a remarkable abnormality with striking respiratory variation was found (figs. 4 and 9). An extremely loud, palpable, click-like first sound would suddenly appear during expiration only to disappear completely during inspiration. It occurred just after the first sound, giving the impression of close splitting. Phonocardiograms showed that this sound was present only in expiration and was synchronous with the second component of a closely split first sound occurring before the onset of the carotid pulse (figs. 4 and 9). Clinically, it was quite unlike the second component of a normally split first sound both in intensity and in that it was maximal at the pulmonary area and not the mitral area or fourth intercostal space.[12] This was confirmed in one of the two cases (case 1, E. B.) when the heart was palpated at operation and the sound appeared to originate in region of the pulmonary valve. It thus appears to be related to the phase of ejection from the right ventricle and not to auriculoventricular valve closure. Because of the great shortening of the isometric contraction phase

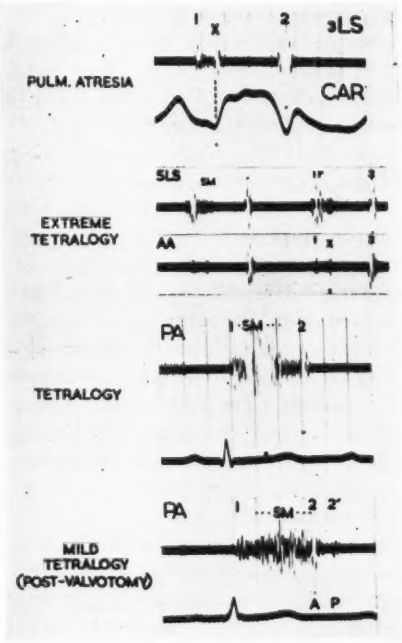

FIG. 12. *The Duration of the Systolic Murmur in Relation to the Severity of Fallot's Tetralogy.* In pulmonary atresia there is usually no systolic murmur. In Fallot's tetralogy with extreme stenosis the murmur is short, soft and confined to early systole. In both these conditions an aortic early systolic sound (X) is usually heard. In the majority of cases of the tetralogy the systolic murmur is loud, reaches its crescendo by midsystole and diminishes rapidly before the loud aortic second sound. In mild cases of the tetralogy the murmur appears to be of longer duration, as shown in the tracing taken six months after a successful valvotomy. The murmur extends up to the aortic second sound (A) but does not obscure it. The pulmonary second sound (P) has become audible, producing wide splitting (0.09 second), indicating Fallot's tetralogy with mild stenosis. (The pulmonary valvotomy has presumably produced a rise in the pulmonary diastolic pressure.)

of the right ventricle, due to the very low pulmonary diastolic pressure, this ejection sound may be almost superimposed on the tricuspid component of the first heart sound. Like the pulmonary early systolic sound in dilatation of the pulmonary artery,[12] this sound is also related to the phase of early ejection from the right ventricle into the pulmonary artery. The mode of production, however, is possibly different. Audible vibrations may be set up by the sudden tautening of the stenotic pulmonary valve bulging into the pulmonary artery at the moment of ejection into the pulmonary artery. This sign is not confined to severe pulmonary stenosis but has also been encountered in moderate and mild stenosis. It was first described by Petit[37] in 1902 and by several workers since.[33, 38, 12, 39] We have not encountered this sign in Fallot's tetralogy.

SUMMARY

1. The differentiation of Fallot's tetralogy from severe pulmonary stenosis with intact ventricular septum and reversed interatrial shunt is important because the surgical treatment is different. While the diagnosis can generally be made on clinical grounds alone, it is usually necessary to confirm the diagnosis by special investigations.

2. A clinical and phonocardiographic study of the heart sounds and murmurs has been made in six cases of severe pulmonary stenosis with intact septum and in 18 cases of Fallot's tetralogy.

3. A striking difference in the behaviour of the systolic murmur *at the site of maximal intensity* was found in the two conditions, if attention was directed to the duration of the systolic murmur in relation to the second heart sound and to the position in systole of its maximal intensity. In Fallot's tetralogy the systolic murmur, however soft or loud, starts soon after the first sound, reaches maximal intensity by mid-systole and then diminishes markedly, usually ending before the single loud, often palpable, aortic component of the second sound. By contrast, in severe pulmonary stenosis with intact ventricular septum, the systolic murmur is so prolonged, that it extends beyond and drowns the normal aortic component of the very widely split second sound. It stops before the delayed, diminutive pulmonary component which may or may not be audible.

4. This significant difference in the systolic murmur so clearly shown by phonocardiography is readily appreciated by the ear and affords a new simple bedside method of diagnosis.

5. Phonocardiographic studies revealed

further points of interest. In severe pulmonary stenosis with intact septum the second heart sound is very widely split due to a diminutive pulmonary second sound being widely separated from the normal aortic component. In Fallot's tetralogy the second sound is usually single because the loud aortic sound is followed by an inaudible pulmonary sound. However, if the pulmonary artery pressure is sufficiently high, this delayed pulmonary second sound becomes recordable and even audible. The mechanism underlying these findings is fully discussed.

6. A presystolic murmur loudest in the left parasternal region was heard in a case of severe pulmonary stenosis with intact ventricular septum and reversed interauricular shunt. It was attributed to flow through the atrial septum or the stenosed pulmonary valve during atrial systole.

7. A loud atrial sound was heard in three cases of severe pulmonary stenosis with intact septum but not in Fallot's tetralogy.

8. In four severe cases of Fallot's tetralogy in whom the murmur was not intense, an early systolic sound was heard which caused "wide splitting" of the first sound. In two cases of severe pulmonary stenosis with intact ventricular septum close splitting of the first sound was heard with an intense clicking second component. The mechanism underlying these findings is discussed.

Summario in Interlingua

1. Le differentiation de tetralogia de Fallot ab sever stenosis pulmonar con intacte septo ventricular e revertite derivation interatrial es importante proque le tractamento chirurgic differe in le duo casos. Ben que le diagnose es generalmente facibile super le base de datos clinic, il es usualmente necessari verificar le diagnose per investigationes special.

2. Esseva executate un studio clinic e phonocardiographic del sonos e murmures cardiac in sex casos de sever stenosis pulmonar con intacte septo e in dece-octo casos de tetralogia de Fallot.

3. Esseva trovate un frappante differentia inter le duo conditiones in le murmure systolic *al sito de intensitate maximal*. Iste differentia esseva manifeste in le relation inter le duration del murmure systolic e le secunde sono cardiac e in le puncto del systole ubi le murmure attingeva su intensitate maximal. In casos de tetralogia de Fallot le murmure systolic—sin reguardo a si illo es forte o basse—comencia tosto post le prime sono; illo attinge su intensitate maximal in mediesystole; e tunc illo diminue marcatemente e se termina usualmente ante le unic e forte e frequentemente palpabile componente aortic del secunde sono. Per contrasto con isto, in casos de sever stenosis pulmonar con intacte septo ventricular, le murmure systolic es si prolongate que illo ultrapassa e inunda le normal componente aortic del secunde sono que alora es nettemente dividite. Illo se termina ante le retardate e minime componente pulmonar que a vices es audibile e a vices non.

4. Iste significative differentia in le murmure systolic, que se demonstra si clarmente per medios phonocardiographic, es facilemente perceptibile per le aure e representa un nove e simple methodo de diagnose clinic.

5. Studios phonocardiographic revelava altere punctos de interesse. In casos de sever stenosis pulmonar con intacte septo, le secunde sono es dividite a longe intervallo in consequentia del facto que un minime secunde sono pulmonar es nettemente separate ab le normal componente aortic. In tetralogia de Fallot le secunde sono es generalmente non-dividite proque le forte sono aortic es sequite per un inaudibile sono pulmonar. Nonobstante, si le pression pulmonoarterial es sufficientemente alte, le retardate secunde sono pulmonar deveni registrabile e mesmo audibile. Le mechanismo al base de iste constatationes es discutite.

6. Un murmure presystolic que habeva su intensitate maximal in le region sinistro-parasternal esseva audite in un caso de sever stenosis pulmonar con intacte septo ventricular e revertite derivation interauricular. Illo esseva attribuite a un fluxo a transverso le septo auricular o a un stenosis del valvula pulmonar durante le systole auricular.

7. Un forte sono auricular esseva audite in tres casos de sever stenosis pulmonar con intacte septo sed non in tetralogia de Fallot.

8. In quatro sever casos de tetralogia de Fallot le murmure non esseva intense, sed il se audiva un prompte sono systolic que causava un division a grande intervallo del prime sono. In duo casos de sever stenosis pulmonar con intacte septo ventricular, un division a breve intervallo esseva audite in le prime sono. Le secunde componente representava un intense clic. Le mechanismo al base de iste constatationes es discutite.

Addendum

Since this paper was submitted we have encountered three further cases of severe pulmonary stenosis with intact ventricular septum and right-to-left interatrial shunt and eight cases of Fallot's tetralogy. In each case a correct diagnosis was made from auscultation alone. Furthermore, in Fallot's tetralogy it was usually possible to assess whether the stenosis was extreme, average or mild by paying careful attention to the auscultatory features discussed above (fig. 12). These cases are discussed elsewhere.[6]

Acknowledgments

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A New Orally Active Quaternary Ammonium, Ganglion Blocking Drug Capable of Reducing Blood Pressure, SU-3088

By KEITH S. GRIMSON, M.D., ANTONE K. TARAZI, M.D., AND JOE W. FRAZER, JR., M.D.

Experiments were performed in animals to evaluate 4,5,6,7-tetrachloro-2-(2 dimethylaminoethyl)-isoindoline dimethochloride, (Su-3088), as an orally effective ganglion blocking drug. These demonstrated reduction of blood pressure, suppression of vasopressor reflexes and potentiation of the pressor action of epinephrine. Neostigmine deblocked drug effects and returned responses toward normal. Experiments in patients produced reduction of blood pressure, warming of extremities and delay of gastric emptying. Preliminary trial as a treatment for hypertension suggested that the drug may be useful. It has a long period of action, 12 hours or more and a small dose requirement, 50 to 100 mg.

OF many ganglion blocking agents developed since tetraethylammonium chloride only two have been sufficiently active with oral administration to justify extensive clinical use. These are hexamethonium bitartrate or chloride and pentolinium tartrate (Ansolysen). Each is a symmetrical compound having six and five carbon chains respectively. A new compound prepared by Huebner and reported by Plummer, Trapold, Schneider and Earl[1, 2] differs in that it is unsymmetrical and has two carbon atoms separating the quaternary nitrogen groups. The compound (fig. 1) is 4,5,6,7-tetrachloro-2-(2 dimethylaminoethyl)-isoindoline dimethochloride.* Plummer demonstrated its ganglion blocking action, found its duration of action twice as long as that of hexamethonium or pentolinium and demonstrated efficient oral activity in dogs. This report describes experiments in dogs to test the ganglion blocking action; it also presents the first clinical testing in man and trial in hypertensive patients.

EXPERIMENTS IN DOGS

Seven acute experiments were performed in dogs weighing 11 to 25 Kg, anesthetized with chloralose, 0.1 Gm. per kilogram, given intravenously. A tracheal cannula was inserted, the carotid arteries isolated, and the vagus nerves divided. The right femoral artery was divided and cannulated proximally. This permitted recording of mean systemic blood pressure, using a mercury manometer.

Respirations were measured by a pneumograph connected to a recording tambour.

After preparation, standard tests of the circulatory system were employed in each animal. Carotid sinus reflexes were elicited by occlusion of both common carotid arteries, using bulldog clamps applied for one minute. Peripheral vagal stimulation was accomplished for 15 seconds, using a tetanizing current from a Harvard inductorium set at 7 or 8 cm. Central vagal stimulation also employed a tetanizing current for 15 seconds but the setting of the inductorium was reduced to 6 or 7 cm. Epinephrine was injected as a 1:10,000 solution through a venous cannula, one gamma per kilogram.

Results

The typical effects of a single injection of Su-3088, 2 mg. per kilogram, are shown in figure 2. Increments up to 2 mg. per kilogram were additive. Additional doses beyond this amount did not significantly enhance any effect. Neostigmine elevated blood pressure and restored pressor reflexes and the cardiac slowing with stimulation of the peripheral vagus. Results of each test are summarized.

Potentiation of Epinephrine. Increase of blood pressure caused by injection of one gamma of epinephrine was measured before and after 2 mg. per kilogram of Su-3088 in four dogs and after 1 mg. per kilogram in three. With 2 mg.

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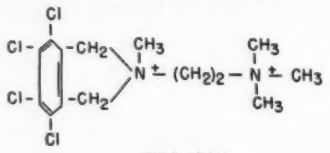
* Supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

4,5,6,7-TETRACHLORO-2-(2-DIMETHYL-AMINOETHYL)-ISOINDOLINE DIMETHOCHLORIDE



(Chloride)
Su-3088

FIG. 1. Chemical name and structural formula of SU-3088.

per kilogram the average of the rise of blood pressure before the Su-3088 was 72 mm. Hg, mean systolic, above a general blood pressure level of 130 mm. After the drug the rise was 85 mm. Hg above a level of 101 mm. The average increase of the height of the rise after the drug was 13 points and the average reduction of general blood pressure level was 29 points. After 1 mg. per kilogram such potentiation was evident in only one of the three dogs. With subsequent doses greater than 2 mg. per kilogram there was no additional increase of the pressor response to epinephrine and no further decrease of general blood pressure.

Carotid Sinus Reflex. The average increase of mean systolic blood pressure with occlusion of both carotid arteries before Su-3088, 2 mg. per kilogram, in four dogs was 51 mm. above a general blood pressure level of 108. After the drug the average increase was 14 mm. above a level of 73 mm. Hg. The average increase before a dose of 1.0 mg. per kilogram in three dogs was 99 mm. above a level of 159 mm. After this dose the increase was 19 mm. above a level of 113 mm.

Stimulation of Central Vagus. The pressor response with stimulation of the central end of one divided vagus nerve was similarly measured. Before 2 mg. per kilogram the average rise was 58 mm. above a level of 128 mm., afterward 23 mm. above a level of 73 mm. The rise decreased 35 mm. and the blood pressure decreased 55 mm. after the drug. With 1 mg. per kilogram the average rise before the drug was 47 mm. above 157 mm. and after the drug the rise was 39 mm. above 115 mm., a lessening of the rise by 8 mm. and of the blood pressure level by 42 mm.

Blood Pressure and Pulse Decrease with Stimulation of the Distal End of the Divided Right Vagus. Four dogs were tested before and after Su-3088, 2 mg. per kilogram. The average blood pressure fell from 130 mm. to 29 mm. before the drug and from 122 mm. to 106 mm. afterward. The average pulse decreased from 192 per minute to 0 to 4 beats in 15 seconds before the drug and from 136 per minute to 124 per minute afterward. Three dogs were tested before and after 1 mg. per kilogram. The average blood pressure fell from 124 mm. to 32 mm. before the drug and from 78 mm. to 61 mm. afterward. The average pulse decrease was from 153 per minute to 0 to 12 beats in 15 seconds before the drug and from 139 to 108 per minute afterward.

Blood Pressure and Pulse. Pulse and blood pressure were selected from the kymograph record at a level point not associated with any stimulus, before and after Su-3088. For four dogs given 2 mg. per kilogram the mean systolic systemic blood pressure averaged 127 mm. Hg before and 100 mm. afterward, pulse 185 per minute before and 133 afterward. For three dogs receiving 1 mg. per kilogram pressure changed from 166 mm. to 113 mm. and pulse from 188 per minute to 136.

Accumulating Doses. Of the seven dogs studied three were given single doses of Su-3088, 1.0 mg. per kilogram and then neostigmine. Four received repeated and progressively increasing doses to a total of 2.5, 8.5, 8.9 and 9 mg. per kilogram. None exhibited curariform or other toxic effects. Supply of the drug was not enough to test larger doses. Initial injections of 0.5, 1 and 2 mg. per kilogram produced prompt reductions of blood pressure of 30 mm. Hg or more. This reduction persisted during three to five hours of observation unless neostigmine was used. Smaller initial doses, 0.001 to 0.05, caused no appreciable effect. Doses of 0.05 mg. per kilogram caused slight reduction of pressure and lessening of the cardiac slowing of stimulation of the peripheral vagus. After a dose of 1 or 2 mg. per kilogram, additional doses of 2 to 5 mg. per kilogram produced slight, transient or no further

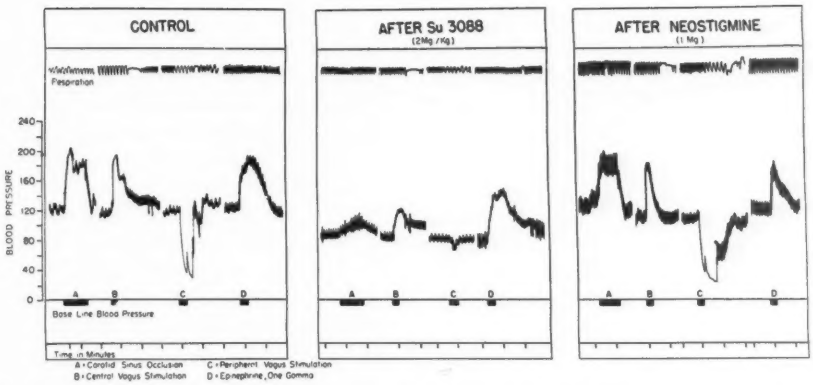


FIG. 2. Standard tests of the circulatory system are shown during the control period before any drug and 20 minutes after intravenous injection of SU-3088, 2 mg. per kilogram. Later after a total accumulative dose of 9.0 mg./kg. and during a 120 minute period of observation the injection of a single dose of neostigmine, 1 mg., deblocked ganglia and restored the tests to their original status during the control period.

reduction of general blood pressure, block of reflexes or potentiation of rise with epinephrine.

Neostigmine Deblocking Effect. Neostigmine methylsulphate was given intravenously, 0.5 mg. to one dog and 1 mg. to another, at the end of two experiments following total accumulative doses of 8.5 mg. per kilogram and 9 mg. per kilogram of Su-3088. General blood pressure promptly rose 30 and 36 mm., slightly exceeding the blood pressure at the start of the experiment. Return of cardiac slowing and of rise with pressor reflexes occurred promptly, responses equalling or exceeding those during the control period at the start of the experiment. The rise with epinephrine continued with little change.

Initial doses of 1.0 mg. per kilogram of Su-3088 were given to three dogs 43 to 55 minutes before intravenous administration of 0.25, 0.5 and 0.5 mg. doses of neostigmine methylsulphate. No additional drugs were then given. Reflexes and cardiac slowing depressed by Su-3088 immediately returned toward normal following neostigmine and the general blood pressure level returned toward its original height. Rise with epinephrine continued higher than before the Su-3088, equal to the potentiation after Su-3088. Following the neostigmine, reflexes and epinephrine were tested at intervals during 150 to 228 minutes. Toward the end of this time period, reflexes were again diminishing in two dogs and were blocked in the third. This evidently represented a wearing off of the neostigmine deblocking effect and a return of the long-lasting blocking effect of the Su-3088. A final dose of neostigmine, 0.25 mg. to 0.5 mg., was then given and restored reflexes to or almost to the original responses, those of the control period before Su-3088.

TESTS IN MAN

Single oral doses of 50 or 100 mg. of Su-3088 have been given to 18 patients on a fasting stomach at 8:30 or 9:00 a.m. Blood pressures with the patient in the supine and also in the upright position were obtained at intervals of 5 to 30 minutes before and for 29 hours after the drug, using a cuff-mercury sphygmomanometer. Pulse and respiration rates were counted. Skin temperature readings were obtained from the umbilicus to toe several times before and during six hours after the drug. Occurrence of side actions such as dilatation of the pupils and dryness of the mouth were noted. Some patients were also given barium by mouth an hour after the drug or several hours afterward and progress of emptying of the stomach was determined by hourly roentgenograms for six hours.

Results:

Blood Pressure. Three normotensive individuals were given Su-3088 orally. One received a 50 mg. dose. Control readings of blood pressure ranged around 100/70 supine and 105/74 standing. Three and a half hours after the drug the supine pressure was 94/72 and the

upright pressure was 88/70. There was minimal blurring of vision and dryness of mouth. Two normotensive individuals were given 100 mg. of Su-3088 orally. They had more pronounced blurring of vision and dryness. Blood pressure in the supine position reduced from 120/74 and 110/60 to 80/70 and 84/54, respectively, reaching their lowest level at about six hours. Postural hypotension prevented standing at three to six hours and this persisted into the night. Temperature of the toes increased. Rate of pulse and respiration did not change.

Eight hypertensive patients were given 100 mg. of Su-3088 orally. One had no significant reduction of blood pressure and did not develop postural hypotension. This patient was one known to tolerate 600 mg. doses of pentolinium four times a day without reduction of blood pressure or blurring of vision. He subsequently required 200 mg. doses of Su-3088 an hour before breakfast for any effects. He is an example of the occasional patient who resists or poorly absorbs quaternary ammonium compounds. An injection of 110 mg. of Su-3088, 2 mg. per kilogram intravenously, produced marked blurring and postural hypotension but no reduction of supine blood pressure.

A second of the eight patients receiving 100 mg. doses had a severe hypertension and a marked cirrhosis of the liver. Subsequently he could not be managed on continuing treatment because of fluctuations of pressure every 8 to 12 hours, periods of elevation to 220/125 alternating with periods of decrease to 130/90 and postural weakness when the pressure was low. Because of the uncertainties related to his cirrhosis and the use of a new drug, treatment was discontinued. With the first test dose his supine blood pressure reduced from 190/120 to 148/96 for 12 hours, upright pressures reduced to 110/90 and blurring of vision developed.

The remaining six patients continue using Su-3088, a single dose of 75 or 100 mg., an hour before breakfast. The initial effect of the test 100 mg. dose for each is shown in figure 3. The supine blood pressure of one patient rose during the first three hours after the drug. His subsequent pressures and those of the other

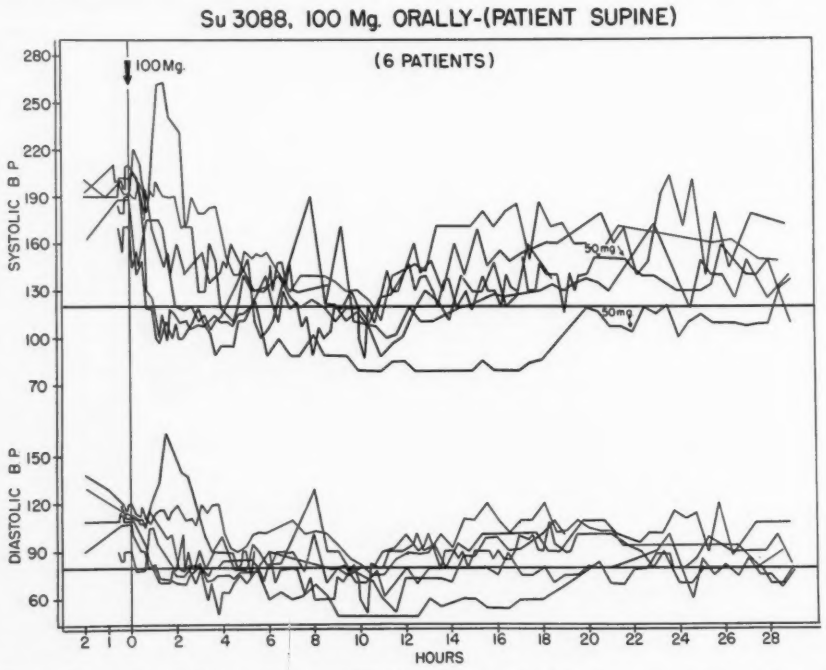


FIG. 3. Effect of ingestion of 100 mg. of SU-3088 on the supine blood pressure of six patients. Reduction of pressure persisted 12 to 29 hours.

patients remained reduced for 12 to 29 hours. Each patient was unable to stand for several hours. Development of postural hypotension is shown in figure 4. During 8 to 16 hours thereafter these patients were unable to stand any length of time without syncope. Fourteen to 21 hours after the drug they still had some postural hypotension.

Seven hypertensive patients were given test doses of 50 mg. of Su-3088 orally. One had no significant reduction of blood pressure or blurring of vision. He subsequently required 200 mg. before side actions and reduction of pressure occurred. This is another example of a patient who resists or poorly absorbs the drug.

A second of the seven patients receiving a 50 mg. test dose also had a severe hypertension with fluctuations of blood pressure on treatment, depressions to around 170/100 lasting five to nine hours alternating with periods of elevation to around 220/130. She finally became stabilized at pressures around 180/124 on two doses a day, 100 mg. an hour before breakfast and 100 mg. an hour and a half after the evening meal. Postural hypotension occurred and persisted throughout her eight days of hospitalization but was not disabling. The first 50 mg. dose produced postural hypotension within 45 minutes. However, the supine pressure which was 212/114 during the control period rose during the first two hours after the drug to a high of 260/155, then reduced to 160/100 for 12 hours.

Five of the seven patients receiving 50 mg. test doses of Su-3088 continue on satisfactory management, using Su-3088, 50 to 75 mg. single doses an hour before breakfast. Each had a mild hypertension which had reduced with rest. Their blood pressures during the control period ranged from 140/80 to 180/96. After the 50 mg. oral dose the pressure ranged from 130/65 to 144/90 lying. Blood pressures in two patients in the erect position were 104/72 and 100/68 five hours after the Su-3088. Pressures were too low to read in three patients since they could not stand without fainting. Hypotensive effects continued during the night and some postural hypotension persisted the next morning.

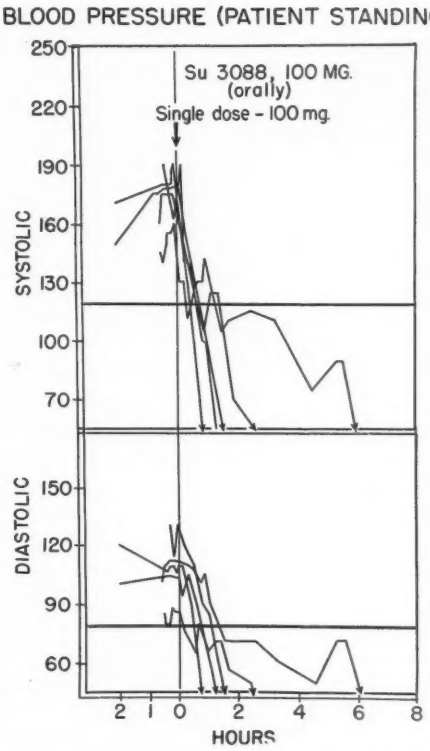


FIG. 4. Development of postural hypotension in five patients following their first test dose of 100 mg. of SU-3088 orally. Marked postural hypotension persisted 8 to 16 hours.

Pulse and Respiration. For the six hypertensive patients receiving 100 mg. test doses of Su-3088 the rate of pulse and respiration averaged 68 and 18 during the control period, 75 and 15 an hour after the drug, 76 and 18 at four hours. For the five receiving 50 mg. test doses the averages were 72 and 16, 74 and 16, and 87 and 16. The highest pulse reading of any patient during the period of hypotension was 100, the lowest 56. One patient exhibited slowing of respiration from 24 to 10 with return to 18 at four hours.

Skin Temperature of a Leg. Four hypertensive patients receiving a 100 mg. test dose orally had measurements of skin temperature from the umbilicus to the great toe. Room temperature ranged from 26 to 27 C. through the test period. The average gradient, umbilicus to great toe, during the control period was 6.5 C. The gradient decreased to 3.2 degrees a

half hour after the drug, 1.1 at one hour, minus 0.1 at two hours, 0.2 at three hours and 0.2 at five hours. Three patients had measurements before and after the 50 mg. oral test doses. The control gradient average was 5.1 degrees. One hour after the drug the average was 2.3, three hours afterward 1.3 and at five hours it was 1.3. In each group of patients dryness and warmth of the skin was still evident at bedtime, 12 to 15 hours after the drug.

Gastric Emptying. Roentgenograms were obtained at hourly intervals for five or six hours following ingestion of barium. The barium was given one hour after ingestion of Su-3088. A light meal was given three hours after the barium. Five patients had received a 100 mg. dose orally. In four, delay of emptying of the stomach caused retention of the barium from 100 per cent to 95 per cent one hour after the barium and two hours after the drug. Delay continued through six hours at which time retention was 80 to 100 per cent. A typical series of roentgenograms is reproduced in figure 5. The fifth patient emptied relatively normally, 60 per cent, 40 per cent, 40 per cent, 30 per cent, 10 per cent and at six hours there was only a trace of barium in the stomach.

Six patients received a 50 mg. dose orally. In five delayed emptying of the stomach caused retention of barium of 95 to 100 per cent at one hour, retention persisting through five or six hours at 85 to 100 per cent. The sixth patient had only 30 per cent at one hour and 10 per cent at two hours. The stomach had emptied normally within three hours. Roentgenograms obtained 24 hours after the drug in three of these patients with delayed emptying revealed barium in the right colon in two and in the lower small intestine and right colon in the third.

Four patients were given barium five to eight hours after the morning dose. They had taken breakfast and lunch. Barium was ingested and films were obtained at hourly intervals starting an hour or two after lunch. One patient emptied rapidly, there being 10 per cent retention an hour after the barium and six hours after his morning dose of 50 mg. of Su-3088. Another patient who had taken a 50 mg. dose nine hours before his roentgenograms had 98 per cent retention one hour after barium, 95 per cent the next hour and 80 per cent an hour later. One who had taken 75 mg. before breakfast seven hours before his roentgenograms had 95 per cent retention one hour after barium and then 90 per cent and 90 per cent. The fourth patient had taken 100 mg. eight hours before his roentgenograms and had 100 per cent retention an hour after barium, 100 per cent an hour later and 100 per cent at the next hour.

Side Actions. Effects on the pupils, salivary glands, bowel movements, urinary bladder and blood pressure with upright posture were described by patients as blurring of vision or photophobia, dryness of mouth, constipation, decreased force of micturition, and dizziness or weakness when standing. These actions of the drug are the effects reported upon the last observations by 11 patients after three to six weeks of treatment and relate to their present dosage schedule, 50, 75, or 100 mg. one hour before breakfast. Side actions of the drug are evident a half hour to an hour and a half after ingestion.

Five patients are taking 50 mg. doses each morning. One cannot read for eight hours. Another has some difficulty in reading for 16 hours. Another has photophobia for five hours. The remaining two have a little difficulty for only two hours. Dryness of mouth is slight in four patients and no dryness is noted by the fifth. Two patients notice a little decrease of force of micturition in the morning. Each patient has experienced weakness with standing lasting most of the day and occurring once or on two or three separate days since starting the drug. Bowel movements occur spontaneously early each morning in four patients and every other morning in the fifth who takes a laxative once a week.

Three patients are taking 75 mg. doses each morning. One cannot read for five hours, two can read but one notices blurring for nine hours and the other photophobia for 10 hours. Dryness of the mouth is slight and no decrease of force of micturition is observed. Each patient notices postural weakness at times in the morning and occasionally sits down or lies down for a few minutes. Bowel movements

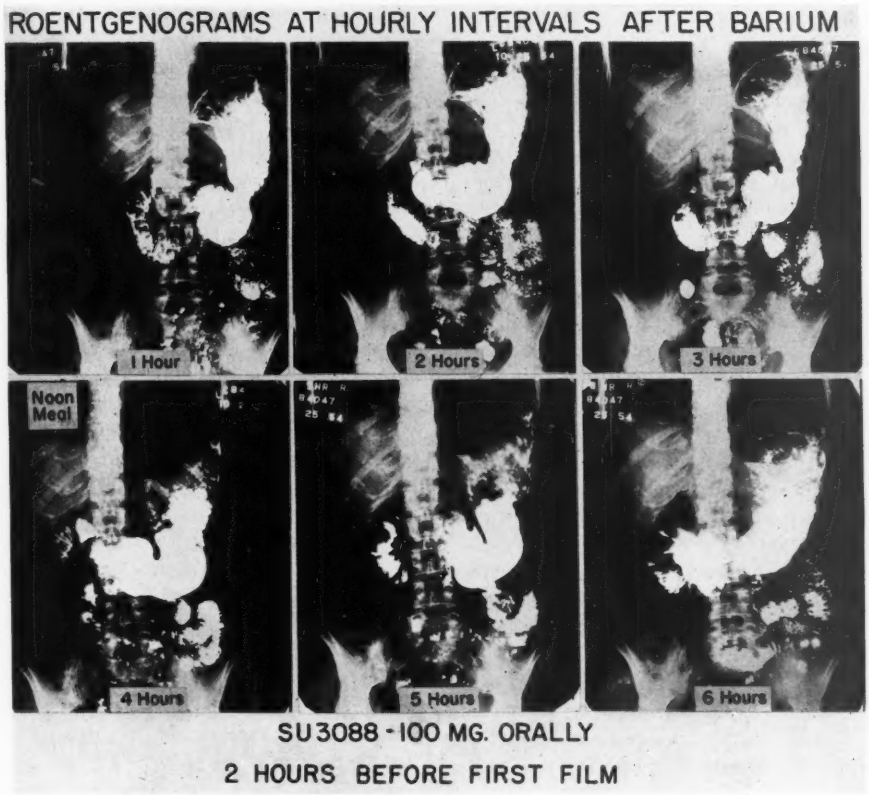


FIG. 5. Hourly roentgenograms starting two hours after taking 100 mg. of SU-3088 orally and one hour after ingestion of barium. Between the third and fourth film a light meal was taken. Delay of rate of gastric emptying was still evident at six hours.

occur each morning in two patients and evening and morning in one. Each takes prune juice, mineral oil or cascara.

Three patients are taking a 100 mg. dose each morning an hour before breakfast. Two cannot read for 12 to 14 hours and are advised to obtain positive correction lenses. One has blurring of vision lasting an hour each morning. Each notices some dryness of the mouth in the morning, little or none in the afternoon. Slowness of the bladder is not noticed. Weakness or dizziness is noticed for one to three hours each morning by two and for a day on two occasions by the third.

DISCUSSION

Su 3088 was developed as a results of experiments by Plummer, Trapold, Earl and Schneider[1, 2] in which a group of bis-quaternary derivatives of dialkyl-amino-alkyl isoindolines were compared for ganglion blocking activity. They found that maximum ganglion blocking potency and maximum oral absorption were associated with interposition of two carbon atoms between quaternary ammonium centers, also with alkylation and quaternization by methyl groups. This led to synthesis of Su-3088. Orally in unanesthetized dogs a dose of 2 mg. per kilogram produced maximum relaxation of nictitating membranes followed by a 50 per cent recovery at 8 to 10 hours and complete recovery at 18 to 20 hours. Decrease of blood pressure occurred and roughly paralleled ganglion blocking activity. Our experiments in anesthetized dogs comfirm the ganglion

blocking actions of Su 3088 and the long duration of action.

Certain of the pharmacological observations have important therapeutic implications. The effective dose intravenously for the dog is 1 to 2 mg. per kilogram. The dose we have found effective in man is similar, 50 to 100 mg. per patient. Absorption is apparently efficient. In the dog and apparently also in man repeated smaller doses add their effects until the optimum dose is reached. After 2 mg. per kilogram, additional doses do not significantly add to reduction of blood pressure or to other actions of the drug. Patients given additional doses of 50 or 100 mg. during the first 10 hours after an effective dose have no increase of hypotension or of side actions. In dogs and in man, reduction of blood pressure in the supine position is to levels around 100 mm. Hg; reduction does not progress to the 80 mm. or lower levels associated with cord section or shock. Patients are comfortable in the supine position even though reduction has occurred from high levels of pressure. This drug evidently has an inherent safeguard in that it suppresses vasopressor reflexes and reduces supine blood pressure to or toward normal without causing troublesome hypotension in the supine position, even with doses which exceed the effective dose.

Two other observations have important therapeutic implications. One is that neostigmine after Su-3088 deblocks ganglia for the duration of the period of action of the neostigmine which is two hours or more. It would not seem logical to recommend neostigmine each morning for bowel movements as is now done for another ganglion blocking drug, pentolinium. All quaternary ammonium compounds tested since our original observation of deblocking effect of Banthine[3] have been deblocked with neostigmine. The second observation is that the typical potentiating effect of the ganglion blocking drug on the pressor effect of epinephrine might explain fluctuations of blood pressure. Occasional rises of pressure are observed on continuing treatment with hexamethonium, pentolinium or Su-3088 and could be explained by the unopposed or increased effectiveness of spontaneously secreted adrenalin. Concomitant use of an adrenolytic drug is under trial.

Testing and clinical trial in 18 patients has demonstrated that Su-3088 causes reduction of supine blood pressure without tachycardia, development of postural hypotension, warming of extremities, mydriasis, decrease of rate of emptying of the stomach and other evidences of partial to complete blockade of ganglia of the sympathetic and parasympathetic division of the autonomic nervous system. Effects develop an hour or more after 50 to 100 mg. doses orally, reach a maximum at six to eight hours, are usually diminishing by 12 to 16 hours and are no longer evident at 24 hours. Constipation, decrease of force of micturition and dryness of the mouth have occurred infrequently or to a minor degree. Delay of emptying of the stomach caused nausea and emesis in four patients receiving their first dose and on one or two other occasions during the first several days of continuing treatment. Otherwise meals were ingested without symptoms. This delay of gastric emptying is an important consideration in planning the timing of subsequent doses since medicine is usually absorbed only when it reaches the intestine. Plummer[4] has found that Su-3088 is stable in gastric juice. Doses given while the stomach is emptying slowly would be slowly absorbed without reaching a high peak blood level. The first dose of the day should be given before breakfast for a good peak level and a maximum blockade. After trying doses before, with and after breakfast it was found that use of the drug an hour before breakfast allows the most accurate adjustment.

Little can be said at the present time concerning results in the 16 patients with hypertension who are now on continuing treatment for three to six weeks. No toxic effects have been observed. Twelve had been taking effective doses of hexamethonium chloride orally. Relief of symptoms has equalled that of hexamethonium and two patients who had experienced some headache in the morning now have none. Each of the 12 prefers Su-3088 for reasons varying from relief of constipation to need to take fewer tablets a day. The greatest

difficulty has been the blurring of vision which may last all day long in some patients even with 50 mg. doses. Postural hypotension is usually present and may be troublesome in the morning. The supine blood pressure is usually reduced. However, even on a standard morning dose the effects may be more pronounced on some days than on others. Each patient has had occasional high and occasional low readings of blood pressure both supine and standing. Trial of use of two or three doses a day has been possible for only a few days because of inadequate supply of the drug.

Results at present seem to indicate that control of blood pressure has been a little more consistent than with pentolinium; certainly effects continue longer and fewer milligrams are required each day. Side actions and variations of effect are similar. It is not yet certain whether a schedule of therapy can be worked out for Su-3088 which will achieve results comparable to those we have obtained with hexamethonium, given orally, for four years. At least this new drug should be a useful addition to the agents now available for control of hypertension and the reduced milligram requirement and decrease in number of tablets needed each day should predict a financial saving for patients.

Summary

Su-3088 is an orally active ganglion blocking agent capable of suppressing pressor reflexes, reducing blood pressure in the supine position and producing postural hypotension for 12 or more hours after the ingestion of a small dose, 50 to 100 mg.

Summario in Interlingua

Esseva executate experimentos animal pro evalutar le efficacia ganglioblocante de 4,5,6,7-tetrachloro-2-(2 dimethylaminoethyl)-isoindolina-dimethochlorido (SU-3088) in administration oral. Le experimentos demonstrava un reduction del pression sanguinee, suppression del reflexos vasopressor, e potentiation del action pressoral de epinephrina. Neostigmina disblocava le effectos del droga e re-establiva le normal del responsas. Experimentos con humanos produceva reduction del pression sanguinee, calefaction del extremitates, e retardation del vacuation gastric. Essayos preliminari in le tractamento de hypertension pare indicar que le droga pote esser de valor in iste campo. Su action es longeve—12 horas o plus—e illo require parve dosages—50 a 200 mg.

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The Effect of Cortisone on Experimentally Produced Myocardial Infarcts

By Norman G. Hepper, M.D., Raymond D. Pruitt, M.D., David E. Donald, B.V.S., M.R.C.V.S., and Jesse E. Edwards, M.D.

Administration of a moderately large or large dose of cortisone to dogs having acute myocardial infarctions inhibited slightly the rate of removal of necrotic muscle fibers in these animals as compared with untreated animals. Delay was appreciable at four and six days after production of the infarct in animals receiving 2.5 mg. of cortisone per kilogram of body weight and at 4, 6, 12 and 21 days in animals receiving 10 mg. per kilogram. At all other periods up to essentially complete healing of the infarcts as defined at 60 days, no appreciable differences existed between treated and untreated animals.

WITH the general availability of cortisone, the study of its influence on such fundamental body reactions as inflammation, connective tissue growth, and immunologic responses has been possible. That administration of cortisone does materially alter these reactions in many animals under certain conditions is now well known.

The lack of information concerning the effect of cortisone on the healing of myocardial infarcts prompted the investigation of this problem in dogs. During the formulation of this problem, two reports on the results of investigations along these lines appeared in the literature.[1, 2] The fact that strikingly different results were obtained by two groups of investigators (Johnson and associates; Chapman and associates) made the problem all the more inviting to pursue.

Johnson and associates[1, 3] reported on the effects of cortisone on experimentally produced myocardial infarcts in dogs. When they gave the animals 25 to 40 mg. of cortisone daily beginning at the time of ligation of the anterior descending coronary artery, they found that the resulting myocardial infarcts were strikingly smaller than were the infarcts in the animals of the control group, which underwent the same operation but did not receive cortisone. They also found fewer adhesions in the surgical area, less postoperative morbidity, a lower mortality rate, and a marked decrease in fibroblastic proliferation in the animals treated with cortisone. Increased vascularity of the infarcts in the treated animals was also noted.

Chapman and co-workers[2] gave 7 mg. of cortisone per kilogram of body weight daily to a group of dogs and ligated the anterior descending coronary artery in its proximal third. Control animals were similarly operated on but did not receive cortisone. Examination of the infarcts in 10 and 30 days disclosed no gross differences between the animals receiving cortisone and the control animals. Slightly less coagulative necrosis was noted in the infarcts in animals which had received cortisone for 30 days than was noted in the control group. No difference in the inflammatory response or in the degree of fibrosis was noted.

Subsequent to a report of our investigation published in abstract form,[4] Opdyke and his associates[5] reported on their attempts to duplicate the experiments of Johnson and coworkers. They found no difference in mortality, in the number of adhesions, or in the size, rate of healing or vascularity of the infarcts between the cortisone-treated and the control animals.

Methods

It was decided that this study should involve 36 dogs. Thus, whenever an animal died, another animal was operated on and given the type of treat-

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Abridgment of thesis submitted by Dr. Hepper to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

ment which the original animal had been designed to have. These 36 mongrel dogs, weighing from 12 to 17 kg., were divided into three equal groups: a group receiving injections of a control solution, a group receiving cortisone intramuscularly in a dose of 2.5 mg. per kilogram of body weight daily, and a group receiving 10 mg. of cortisone per kilogram of body weight daily. In those animals receiving cortisone, administration of the drug was begun 48 hours prior to the operation to be described and was continued until death, the last injection being given within 16 hours of the time of death. The total daily dose was administered in two equal injections.

The same schedule was followed in injecting animals of the control series save that in the place of the cortisone solution a solution was used which contained, except for carboxymethylcellulose, all of the agents of the suspending vehicle of "cortone" in similar concentrations.

With the animals under ether anesthesia myocardial infarcts were produced by ligating the anterior descending coronary artery. This was done at such a distance from the origin of the artery that the area of myocardial cyanosis which appeared involved the anterior surface of about the apical third of the left ventricle.

Ligation of secondary, tertiary or large anastomotic communications was done occasionally in an effort to produce the desired area of myocardial cyanosis. The average distance of the point of ligation from the origin of the anterior descending coronary artery was 3 cm.

The technic of ligation included the method described by Harris,[6] which involves constricting, for a period of time, the coronary artery to be ligated in an attempt to reduce the incidence of fatal arrhythmia which may occur at the time of complete interruption of the artery.

At the selected point the artery was isolated and then constricted by ligating it over a 20 gage needle. The needle was immediately extricated with a resultant reduction in the diameter of the lumen of the vessel to that of the outside diameter of the needle. This constriction was maintained for an average of 22 minutes in 35 of the 36 experiments. In one animal, the artery was ligated abruptly. During the period of constriction a segment of artery below the ligature, varying in length between 0.8 cm. and 2.5 cm. (average, 1.4 cm.), was isolated. Following the period of constriction this isolated segment was ligated and excised so that any communicating channels which might bypass a single ligature were disrupted.

The pericardium was then closed after 100,000 units of crystalline penicillin had been instilled into the pleural and pericardial spaces. Each animal was given 300,000 units of depot penicillin intramuscularly at the time of operation and daily for two days thereafter except for those animals in which the experiment was terminated in two days. In this case the injection of the second day was omitted.

At 2, 4, 6, 12, 21 and 60 days after the operation at which myocardial infarction was produced, two animals from each of the three treatment groups were killed either by an overdose of ether or by exsanguination while the animals were anesthetized, and the infarcts were studied in the manner to be described. Necropsy was performed immediately after death.

Sections of the hearts were stained variously, depending on the age of the infarct. Sections from two-day-old infarcts were stained only with hematoxylin and eosin. Those from four-day-old infarcts were stained with hematoxylin and eosin, Mallory-Heidenhain and Mallory's phosphotungstic acid hematoxylin stains. Sections from the 6 and 12-day-old infarcts were stained, in addition, with van Gieson's connective tissue stain. Sections from the 21 and 60-day-old infarcts were stained with the same stains except that van Gieson's stain was replaced by Verhoeff's elastic tissue stain with a van Gieson counterstain.

The sections from the infarcts in animals of the control group were studied first. The features of the healing processes at the different age intervals were noted. Then the identifying labels on all slides from the infarcts of animals having received cortisone were covered so that the microscopic examination of the sections was made without knowledge as to the age of the particular infarct being studied or the dosage of cortisone which the animal had received. In this part of the examination an attempt was made to estimate the age of the infarcts as a means of judging whether the rate of healing was different or similar to that of the infarcts in the control group. Then, all slides from the infarcts of the six animals in each age group including the controls were studied as unknowns and the healing processes were compared.

Results

The mortality rate in this series was 14.3 per cent. Of the six animals that died, five had received cortisone and one was a control. Of the five deaths occurring during operation, four resulted from ventricular fibrillation and one from ventricular standstill. One death occurred six hours after operation. Of the 42 animals operated on, 29 had been treated with cortisone and 13 were controls.

All of the surviving animals tolerated the surgical procedure remarkably well, and no consistent difference in postoperative recovery rate was noted between the cortisone-treated and the control animals.

One animal, in the group receiving the larger

FIG. 1. A two-day-old infarct in one of the animals receiving 10 mg. cortisone per Kg. of body weight daily. The heart has been sliced transversely parallel to the base. Each slice is approximately 1 cm. thick. Infarcts of this rather large size were produced in both cortisone-treated and non-cortisone-treated animals.

dose of cortisone for 62 days, had to undergo reoperation on two occasions because of separation of the deeper layers of the thoracic incision. This animal received penicillin daily over a longer period of time than did the other animals comprising this study. The incision eventually healed satisfactorily while the animal continued to receive cortisone.

As mentioned in the section devoted to the description of methods, the microscopic sections from the infarcts were studied as unknowns by two methods.

First, the labels on the slides from the infarcts of all animals having received cortisone were covered, and the slides were studied as unknowns. These were properly identified as to age, with the following exceptions: The six-day-old infarcts of the animals receiving the larger doses of cortisone were incorrectly interpreted as being infarcts of four days' duration. Also, the four-day-old infarcts, both of the group with the smaller and of the group with the larger doses of cortisone, while interpreted as four-day-old infarcts, seemed to have less evidence of removal of necrotic muscle than had the 4-day-old infarcts of the control animals.

Secondly, the infarcts from the six hearts in each age group were compared grossly and microscopically without knowledge to which treatment group each specimen belonged. Later the key was exposed, allowing comparison to be made. The following results were obtained from this second method of study.

Two-day-old Infarcts. There was no difference in the amount of fibrinous exudate on the pericardial surfaces, in the appearance of the necrotic muscle, in the degree of polymorphonuclear infiltration, or in the number of extravasated erythrocytes among the infarcts of the cortisone-treated as compared to the control group (fig. 1). The very minimal degree of resorption of necrotic fibers which was observed in the control group was not seen in either of the treated series.

Four-day-old Infarcts. No gross differences between the infarcts of animals receiving cortisone and those not receiving cortisone were noted. Microscopically, resorption of necrotic muscle in the hearts of all animals receiving cortisone was somewhat less than in the controls (fig. 2*a* and *b*). The dose of cortisone apparently did not influence the degree of inhibition of resorption. There was no appreciable difference in the degree of polymorphonuclear infiltration or in the number of mitotic figures among fibroblasts in the cortisone-treated as compared with the control subjects.

Six-day-old Infarcts. Grossly, the narrow gelatinous zone, the zone of resorption immediately peripheral to the necrotic mass of muscle, did not appear to be as wide in the infarcts of dogs receiving 10 mg. of cortisone per kilogram of body weight daily as in the control group. No difference was noted in this respect between the control group and the group receiving the smaller dose of cortisone.

This was confirmed microscopically by a narrower zone from which muscle fibers had been removed in the animals receiving 10 mg. of cortisone per kilogram of body weight daily (fig. 2*c* and *d*). The sections from the group receiving 2.5 mg. of cortisone per kilogram of body weight daily showed a similar but less evident deficiency in removal of necrotic muscle fibers as compared with the controls. With the aid of special stains it was established that there was slightly less collagen formation in the

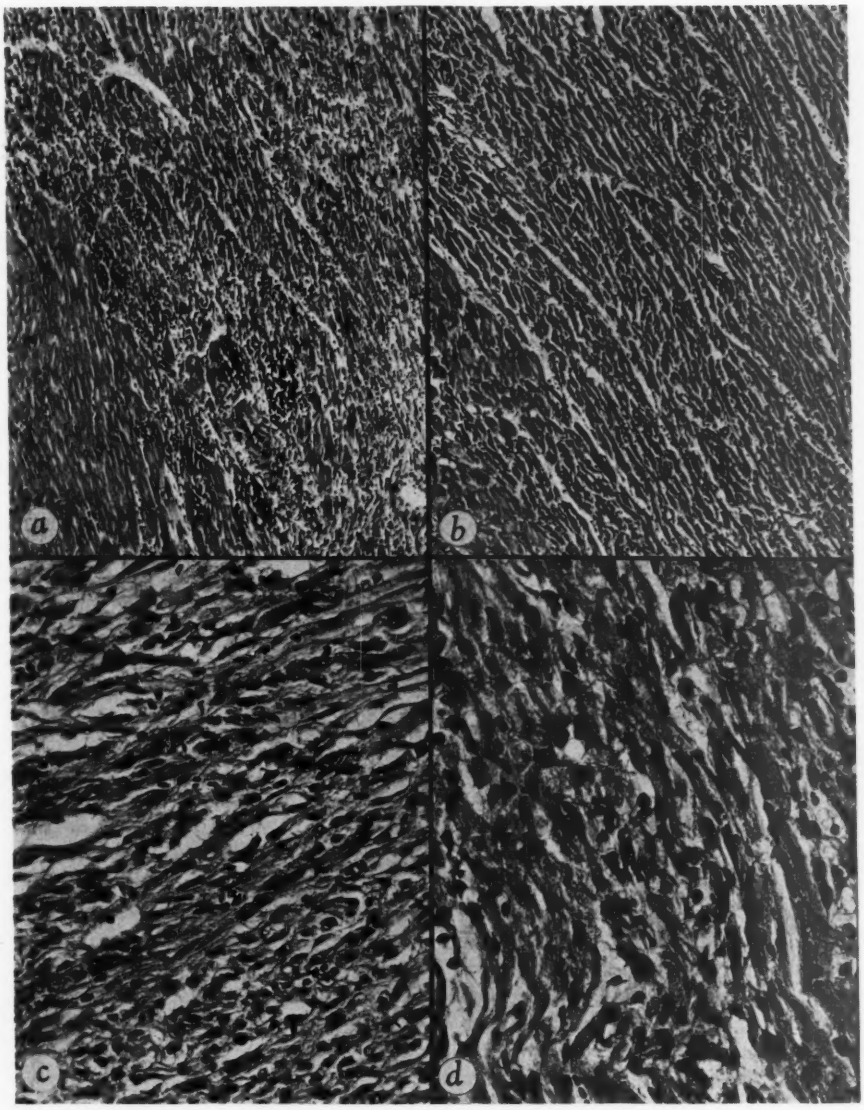

FIG. 2. Comparison of the degree of healing in four and six-day-old infarcts in cortisone-treated and non-cortisone-receiving animals. *a* and *b*. Four-day-old infarct. Zone of resorption next to surviving myocardium which appears on left side of the illustrations. *a*. Control. Note that resorption of necrotic muscle has occurred in the infarcted area (hematoxylin and eosin; ×80). *b*. 10 mg. cortisone per kilogram. Compared to *a*, there has been less resorption of necrotic muscle (hematoxylin and eosin; ×80). *c* and *d*. Zone of resorption and fibroplasia in six-day-old infarcts. *c*. Control. Demonstrates the almost complete absence of necrotic muscle and the condensation of stroma in the most active area of repair (hematoxylin and eosin; ×275). *d*. 10 mg. cortisone per kilogram. The area presented here corresponds to that in *c*. Necrotic muscle still remains and there has been less condensation of stroma (hematoxylin and eosin; ×300).

peripheral portions of the infarcts of the animals receiving the larger dose of cortisone than in the other two groups. No difference regarding collagen formation was observed between the infarcts of the control animals and of the animals receiving the smaller dose of cortisone.

Twelve-day-old Infarcts. The features of the infarcts from the animals receiving the smaller dose of cortisone were no different than those of the controls. In the animals receiving the larger dose of cortisone necrotic muscle had not been removed from as large an area as it had in the controls. Condensation of stroma and collagen formation were, however, qualitatively similar.

Twenty-one-day-old Infarcts. Grossly, in all infarcts of cortisone-treated animals, some necrotic muscle was still identifiable. No other gross differences were observed.

No microscopic differences in the nature and size of the scar were noted between the controls and the group receiving the smaller dose of cortisone, save for the presence of some unremoved infarcted muscle in the latter. Although the infarcts of the two animals receiving the larger dose of cortisone differed slightly between themselves in degree of scar formation, it was felt that in each it was slightly less as compared to that in the controls. The scar tissue present was as densely collagenized as in the controls.

Sixty-day-old Infarcts. There were no essential differences grossly or microscopically between the infarcts of cortisone-treated and control animals. The infarcts in the two control animals were smaller in size than those in the animals receiving cortisone. All infarcts were healed and in all there was much dense collagen. Elastic tissue fibers were present in all scars of this age group.

Comment

A study such as this could only be undertaken once it had been established that the healing processes in experimentally produced infarcts in dogs follow a consistent and predictable pattern with definite time relationships. The close similarity in the degree of healing observed between the two control animals of each age group and the two animals in each cortisone-treated age group established this fact and so permitted the more detailed comparisons between the cortisone-treated and the control groups.

That the healing processes in experimentally produced myocardial infarcts in dogs have a predictable relationship with age is further borne out by the fact that the pattern of healing of infarcts in the control series in this experiment correlates well with that reported in dogs by Karsner and Dwyer.[7] Certain exceptions were observed. It was thought that most of these exceptions were attributable to the larger size of the infarcts in this study as compared to theirs. The microscopic findings in this series of infarcts compared quite well with those described by Mallory and associates[8] in man except that healing proceeded at a considerably more rapid rate in the infarcts of the canine hearts composing this investigation.

Any attempt at standardization of the size of experimentally produced myocardial infarcts would be fraught with much disappointment. The vagaries of the arterial circulation to any area of the heart make the size of the infarct resulting from ligation of a given artery quite variable. It was believed that ligation of the anterior descending coronary artery and inclusion of more or less of the vessel or its branches as needed to produce an area of cyanosis which included the anterior apical portion of the left ventricle would come closer to producing a standard-sized infarct than routine ligation at any given level. This method was here employed.

Cortisone had no appreciable influence on the degree or type of cellular infiltration at any stage of healing. It likewise had no effect on the vascularity of infarcts which could be detected microscopically.

Cortisone in either dosage delayed the healing processes, but only at certain phases. This retardation in healing resulted from delay in the removal of necrotic muscle from the infarct. This delay in removal of infarcted fibers could not be related to reduced numbers of neutrophils or macrophages, since these cells appeared to be present in as large numbers in the cortisone-treated as in the control series.

Cortisone did not have any appreciable

effect on fibroplasia as determined by the cellularity, by the number of mitotic figures, or by collagen formation once an area had been cleared of necrotic muscle. The density of the scar tissue formed was essentially the same in treated animals as in controls.

The results of this investigation do not confirm the findings of Johnson and associates that cortisone has a marked effect on the size and healing of myocardial infarcts. They do, in essence, substantiate the observations of Chapman and co-workers. The larger dose of cortisone employed in certain of the experiments reported here probably accounted for the greater disturbance in healing noted in these experiments than in those described by Chapman's group.

Summary and Conclusions

In this investigation, 36 mongrel dogs were divided into three equal groups: a group receiving injections of a control solution, a group receiving 2.5 mg. of cortisone, and a group receiving 10 mg. of cortisone intramuscularly per kilogram of body weight daily. At 2, 4, 6, 12, 21 and 60 days after the operation at which myocardial infarction was produced by ligating the anterior descending coronary artery, two animals from each group were killed and the infarcts were studied pathologically.

When the infarct was two days old, neither dose of cortisone had disturbed healing appreciably. By four and six days cortisone, in the dose of 2.5 mg. per kilogram of body weight, had inhibited slightly the removal of necrotic muscle fibers as compared with untreated controls. This delay could not be appreciated grossly. At all other intervals studied, infarcts in the animals receiving this dose of cortisone did not differ from the control group.

Cortisone, in a dose of 10 mg. per kilogram of body weight daily, delayed to a small but noticeable degree the healing of infarcts at 4, 6, 12 and 21 days. At four days the delay in resorption of necrotic muscle was no greater than in the group receiving the smaller dose of cortisone and could not be appreciated grossly. At six days the delay in healing was somewhat greater than in the group receiving the smaller dose of cortisone and could be appreciated grossly. The inhibition noticed at four and at six days was the greatest in degree among all the experiments. At 12 days a difference, minor but yet appreciable, was noted between the infarcts in the control group and in the group receiving the larger dose of cortisone. On microscopic examination removal of necrotic muscle and scar formation had been delayed in the latter group as compared to controls. At 21 days the larger dose of cortisone questionably delayed healing, whereas at 60 days all infarcts in the control and cortisone-treated series appeared to be equally well healed.

Summario e Conclusiones in Interlingua

In 36 canes bastarde infarctos myocardiac esseva producite per ligar le descendente arteria coronari anterior. Le canes esseva dividite in tres gruppos equal. Duo gruppos recipeva diurne injectiones intramuscular de 2,5 e 10 mg respectivemente de cortisona per kg de peso corporee. Le tertie gruppo recipeva injectiones de un solution de controlo. A periodos de 2, 4, 6, 12, 21, e 60 dies post le production del infarctos, sex canes (duo de cata gruppo) esseva sacrificate e studiate pathologicamente.

Quando le infarctos habeva un etate de duo dies, ni le un ni le altere dosage de cortisona habeva disturbate le processo curative a un grado appreciabile. Post quatro e sex dies, le dosage de 2,5 mg cortisona per kg de peso corporee habeva exercite un leve effecto inhibitive super le resorption del necrotic fibras muscular in comparation con le stato del animales de controlo. Iste retardation non esseva grossiermente appreciabile. A omne le altere periodos studiate, le infarctos del animales de iste gruppo (2,5 mg cortisona per kg peso corporee) non se distingueva de illos del gruppo de controlo.

In le dosage de 10 mg per die per kg peso corporee, cortisona retardava a un leve sed sensibile grado le curation del infarctos post 4, 6, 12, e 21 dies. Post quatro dies le effecto inhibitive del cortisona super le resorption de musculo necrotic non esseva plus grande in iste gruppo que in le gruppo con le plus parve dosage. Illo non esseva grossiermente appreciabile. Post sex dies le retardation del curation

esseva alique plus grande in iste gruppo que in le gruppo con le plus parve dosage e poteva esser grossiermente appreciate. Le inhibition notate post quatro e sex dies esseva le plus grande inter omne le experimentos. Post 12 dies un minor sed ancora appreciabile differentia esseva notate inter le infarctos del gruppo de controlo e illos del gruppo con le plus grande dosages de cortisona. Le examine microscopic revelava in iste ultime gruppo un retardation del resorption de musculo necrotic e del cicatrisation. Post 21 dies le retardate curation causate per le plus grande dose de cortisona esseva questionabile. Post 60 dies omne le infarctos in tanto le gruppo de controlo como etiam le gruppos tractate con cortisona pareva equalmente ben curate.

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The Functional Circulatory Consequences of Myocardial Infarction

A Biostatistical Analysis Following Wiggers' Schema

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An analysis of what proportion of patients hospitalized with myocardial infarction follow the various circulatory pathways available and at what time in the course of the disease is presented. Patients who died with, but not necessarily because of, thrombosis or embolism outside the coronary vascular bed were withdrawn from the analysis. Almost half of the patients were able to resume usual or lighter activity and to enjoy, after two years, a survival rate similar to a Tennessee population of the same age, sex and racial distribution.

THE measure of a master is his success in bringing all men round to his opinion 20 years later".[1] Some three decades ago Wiggers[2] schematized (fig. 1) the functional circulatory consequences of myocardial infarction on the basis of "clinical and laboratory experience which had grown side by side" up to that time. The acceptance of this formulation has widened during the intervening years to a clinical concept and an aid in teaching. The sequential changes, singly or in combination, have been explored and reported in the literature. An analysis of what proportion of patients follow the various pathways and at what time in the course of the disease has not previously been done in any comprehensive way. Data to derive such an analysis from a hospital population embracing a particular geographical area were available to us from our continuing study of the natural history of coronary artery disease which we have been pursuing since 1945.[3-7]

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A preliminary report of this work was presented at the Salt Lake City meeting of The American Physiological Society, September, 1951.

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Materials and Methods

In the 397 hospital patients studied, the diagnosis of acute myocardial infarction met one or more of the following criteria: (1) typical clinical manifestations with characteristic or compatible electrocardiographic changes, (2) compatible clinical manifestations with unequivocal electrocardiographic changes or (3) autopsy evidence. Data from hospital records were coded and transferred to International Business Machine punch cards, making available over 500 particulars concerning each patient's symptoms, physical findings, and laboratory examinations at the time of the attack, within one week, within one month, and, for those who survived the acute episode, the degree of activity resumed. The ratio of males to females was 3 to 1 in the 355 white patients studied at Vanderbilt University Hospital. The peak age group for males was the sixth decade; for females, the seventh. The 42 Negro patients selected at Meharry Hubbard Hospital, Thayer VA Hospital and Vanderbilt University Hospital matched the white series with respect to male-female ratio and age at the time of the acute episode. In this small selected Negro series no racial differences in the pattern of functional circulatory consequences were apparent.

Fifty-five episodes terminated fatally with associated clinical or autopsy evidence of thrombosis or embolism other than coronary. These patients were withdrawn from the analysis to eliminate as much as possible the area of confusion between consequences of a circulatory functional nature and those attributable to the end results of thrombosis or embolism outside the coronary vascular bed. The

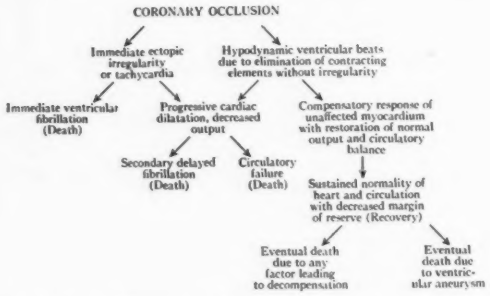
CORONARY OCCLUSION
Immediate ectopic irregularity or tachycardia
Hypodynamic ventricular beats due to elimination of contracting elements without irregularity
Immediate ventricular fibrillation (Death)
Progressive cardiac dilatation, decreased output
Compensatory response of unaffected myocardium with restoration of normal output and circulatory balance
Secondary delayed fibrillation (Death)
Circulatory failure (Death)
Sustained normality of heart and circulation with decreased margin of reserve (Recovery)
Eventual death due to any factor leading to decompensation
Eventual death due to ventricular aneurysm

FIG. 1. Wiggers' schema of sequential changes following coronary occlusion.

TABLE 1.—*Incidence of various evidences of hypodynamic circulation within one week of acute episode of myocardial infarction*

Cardiomegaly	60%	Ankle edema	22%
Fall in blood pressure	51%	Gallop rhythm	22%
Pulmonary Congestion (râles)	49%	Pulse pressure <25 mm. Hg	15%
Congestive heart failure	37%	Frank circulatory collapse, "shock"	15%
Cyanosis	33%	Venous distention	14%
Dyspnea	32%	Generalized edema	8%
Hepatomegaly	31%	Ascites	7%
Weak or thready pulse	30%		

TABLE 2.—*Incidence of arrhythmias observed within one month of the acute episode of myocardial infarction*

Tachycardia (pulse rate > 110)	33%	Bigeminy	5%
Ventricular extrasystoles	24%	First degree heart block	4%
Ventricular fibrillation*	17%	Auricular flutter	2%
Auricular fibrillation	11%	Pulsus alternans	2%
Auricular extrasystoles	9%	Right bundle branch block	2%
Bradycardia (pulse rate <60)	9%	Ventricular tachycardia	2%
Left bundle branch block	6%	All other	9%

* Clinical judgment of terminal episode.

remaining 342 patients comprise the sample for analysis.

A few patients were in the hospital at the time of the attack, the others were hospitalized 6 hours to 16 days after the onset of symptoms. The patterns followed by the specific number of patients seen at the various time periods were tabulated. The group analyzed, 100 per cent, is a composite of these enumerations less those who died with, but not necessarily because of, thrombosis or embolism outside the coronary vascular bed. For example, 242 (81 per cent) of the patients hospitalized within one week survived. Thirty-two patients were admitted one week after the onset of the acute episode and it was assumed that they also represented an 81 per cent one-week survival. The total 274 patients observed at one week reflect an 81 per cent survival among a theoretical group of 338 patients. Similar adjustments in the denominator used to calculate percentages were made at the various time intervals with reference to the population analyzed as 100 per cent.

RESULTS

Hypodynamic ventricular beats due to elimination of contracting myocardial elements as a consequence of myocardial infarction can be detected in experimental circumstances by appropriate recording instruments. In a patient the existence of "hypodynamic" ventricular activity reveals itself by clinical manifestations of heart failure, the "circulatory collapse" variety, the congestive sort or by a mixture of these.

Within the first week, hypodynamic circulation (table 1) in half the cases was evidenced by cardiomegaly, fall in blood pressure, and rales. About one-third of the patients presented each of the following findings: congestive heart failure, cyanosis, dyspnea, hepatomegaly, and weak or thready pulse. Ankle edema, gallop rhythm, "shock", pulse pressure of less than 25 mm. Hg and venous distention were less common. Generalized edema and ascites occurred in less than 10 per cent.

A pulse rate of more than 110 and ventricular extrasystoles were the most frequently noted arrhythmias (table 2). Transient ventricular fibrillation was not detected among these patients. Incidence of this arrhythmia is based upon a study of the terminal episode. A judgment that death was probably due to, or compatible with, ventricular fibrillation could include cases of cardiac arrest. Thromboembolism is a frequent cause of sudden death but cases associated with this complication were eliminated from the analysis as mentioned

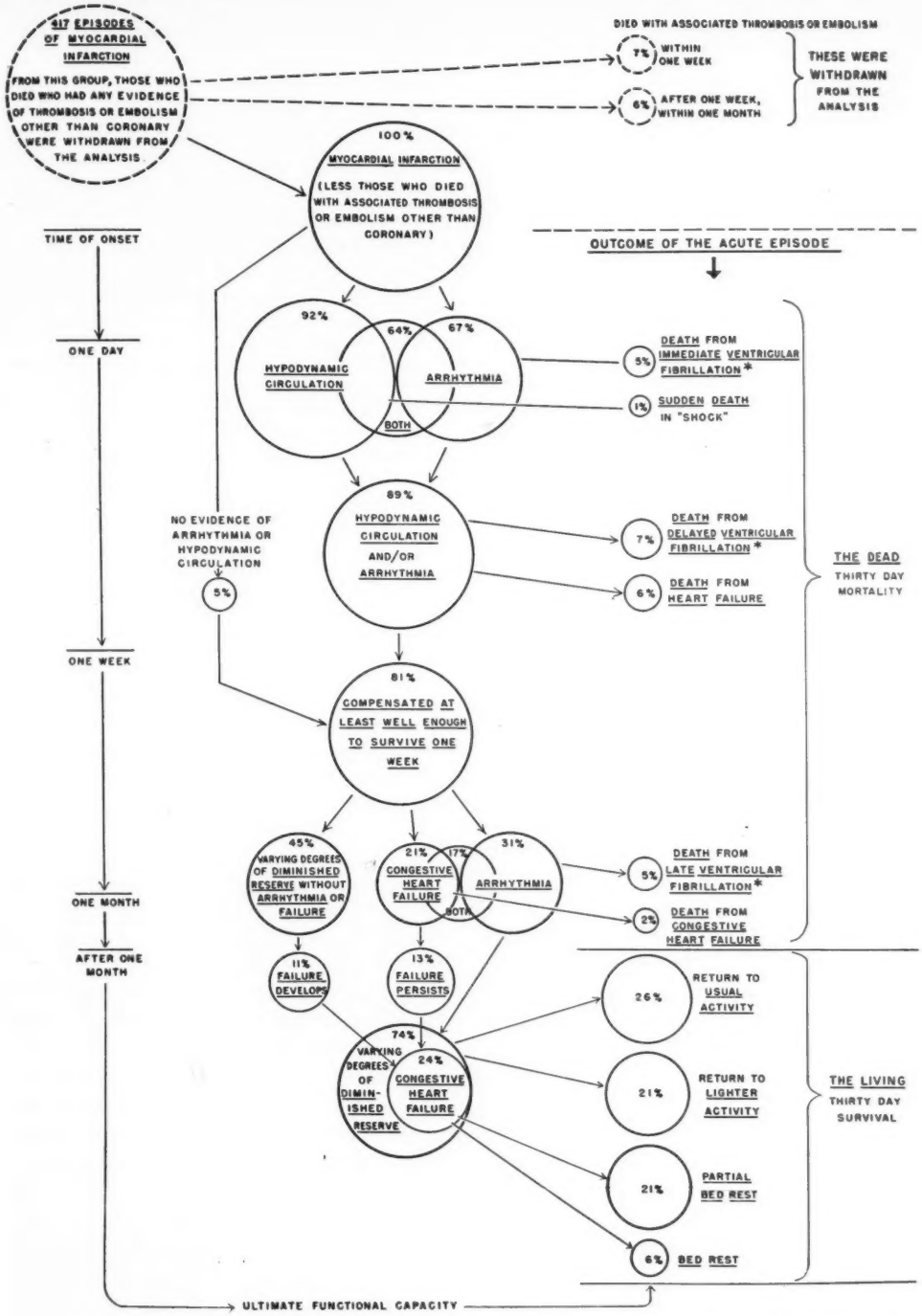
817 EPISODES OF MYOCARDIAL INFARCTION
FROM THIS GROUP, THOSE WHO DIED WHO HAD ANY EVIDENCE OF THROMBOSIS OR EMBOLISM OTHER THAN CORONARY WERE WITHDRAWN FROM THE ANALYSIS
DIED WITH ASSOCIATED THROMBOSIS OR EMBOLISM
7% WITHIN ONE WEEK
6% AFTER ONE WEEK, WITHIN ONE MONTH
THESE WERE WITHDRAWN FROM THE ANALYSIS
100% MYOCARDIAL INFARCTION (LESS THOSE WHO DIED WITH ASSOCIATED THROMBOSIS OR EMBOLISM OTHER THAN CORONARY)
TIME OF ONSET
ONE DAY
ONE WEEK
ONE MONTH
AFTER ONE MONTH
OUTCOME OF THE ACUTE EPISODE
92% HYPODYNAMIC CIRCULATION
64% BOTH
67% ARRHYTHMIA
5% DEATH FROM IMMEDIATE VENTRICULAR FIBRILLATION *
1% SUDDEN DEATH IN "SHOCK"
NO EVIDENCE OF ARRHYTHMIA OR HYPODYNAMIC CIRCULATION
5%
89% HYPODYNAMIC CIRCULATION AND/OR ARRHYTHMIA
7% DEATH FROM DELAYED VENTRICULAR FIBRILLATION *
6% DEATH FROM HEART FAILURE
THE DEAD THIRTY DAY MORTALITY
81% COMPENSATED AT LEAST WELL ENOUGH TO SURVIVE ONE WEEK
45% VARYING DEGREES OF DIMINISHED RESERVE WITHOUT ARRHYTHMIA OR FAILURE
21% CONGESTIVE HEART FAILURE
17% BOTH
31% ARRHYTHMIA
5% DEATH FROM LATE VENTRICULAR FIBRILLATION *
2% DEATH FROM CONGESTIVE HEART FAILURE
11% FAILURE DEVELOPS
13% FAILURE PERSISTS
74% VARYING DEGREES OF DIMINISHED RESERVE
24% CONGESTIVE HEART FAILURE
26% RETURN TO USUAL ACTIVITY
21% RETURN TO LIGHTER ACTIVITY
21% PARTIAL BED REST
6% BED REST
THE LIVING THIRTY DAY SURVIVAL
ULTIMATE FUNCTIONAL CAPACITY

FIG. 2. Proportion of patients with various clinical manifestations of hypodynamic circulation and arrhythmias at onset, at one day, one week and one month following myocardial infarction with the level of activity resumed by survivors.

* Clinical judgment of terminal episode.

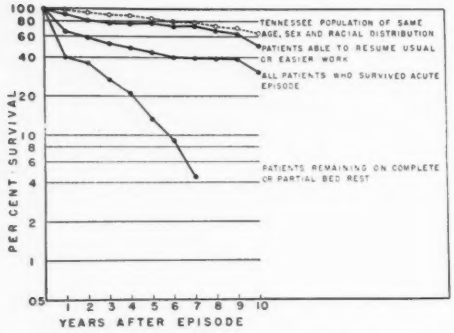

FIG. 3. Survival following myocardial infarction.

above, reducing somewhat this source of uncertainty.

Referring to the population analyzed as 100 per cent (fig. 2), within the first 24 hours, 92 per cent of the patients had clinical manifestations of hypodynamic circulation, 67 per cent arrhythmia, and 64 per cent both hypodynamic circulation and arrhythmia. Five per cent died of immediate ventricular fibrillation, 1 per cent of "shock." In 5 per cent of the cases neither arrhythmia nor hypodynamic circulation was detected within the first week. Of the 89 per cent evidencing hypodynamic circulation and/or arrhythmia at this time, 7 per cent died from delayed ventricular fibrillation, 6 per cent from heart failure. Eighty-one per cent were compensated at least well enough to survive one week.

After the first week and within the month (fig. 2) 45 per cent had varying degrees of diminished reserve without arrhythmia or failure. Twenty-one per cent had definite congestive heart failure, 31 per cent had arrhythmia and 18 per cent had both. Death from late ventricular fibrillation occurred in 5 per cent, from congestive heart failure in 2 per cent. The total mortality within the first month following the acute episode was 26 per cent.

Seventy-four per cent with varying degrees of diminished reserve or impaired function survived the first month (fig. 2). Twenty-four per cent had congestive heart failure, developing after one month in 11 per cent, persisting after one month in 13 per cent. Within a few months 26 per cent of all patients were able to return to usual activity, 21 per cent to lighter activity, 21 per cent remained on partial bed rest and 6 per cent on complete bed rest.

About one-half of all patients were able to resume usual or lighter activity. After three years this group's mortality rate paralleled the Tennessee population of the same age, sex and racial distribution (fig. 3). The outlook was bleak for patients confined to complete or partial bed rest.

SUMMARY

Among hospitalized patients where death was not associated with thrombosis or embolism outside the coronary vascular bed, the mortality from functional circulatory consequences of myocardial infarction within one month of the acute episode was 26 per cent. Death was compatible with ventricular fibrillation in 17 per cent, due to heart failure in 8 per cent, and, within the first 24 hours, sudden death occurred from "shock" in 1 per cent.

The prognosis for the survivors who were able to resume usual or lighter activity was good. For those confined to partial or complete bed rest because of diminished cardiac reserve the prognosis was significantly poor.

SUMMARIO IN INTERLINGUA

Es presentate un analyse biostatistic de un serie de 342 patientes con infarcimento myocardiac. Le serie non include 55 casos mortal associate con evidentia clinic o autoptic de thrombosis o embolismo non coronari.

Le mortalitate debite a consequentias circulatori functional de infarcimento myocardiac intra un mense post le episodio acute esseva 26 pro cento. Morte esseva compatibile con fibrillation ventricular in 17 pro cento del casos; in 8 pro cento illo esseva debite a dysfunctionamento cardiac; illo occurreva subitemente in consequentia de "choc" durante le prime 24 horas in 1 pro cento.

Le prognose pro le superviventes capace a recomenciar normal o reducite activitate esseva bon. Illo esseva significativemente inferior pro le patientes qui esseva completemente o partialmente allectate a causa de lor diminuit reservas cardiac.

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Complications Following Infundibular Resection in Fallot's Tetralogy

By MALCOLM C. MCCORD, M.D. AND S. GILBERT BLOUNT, JR., M.D.

Two patients are presented to demonstrate complications that may arise following infundibular resection in patients with the tetralogy of Fallot. An aneurysm of the infundibular chamber developed in one patient following removal of the infundibular stenosis. A left to right blood flow at the ventricular level occurred postoperatively in a second patient with marked cardiac enlargement and left ventricular hypertrophy.

THE introduction of the Blalock-Taussig procedure in 1945 resulted in a dramatic change in the prognosis of patients with the tetralogy of Fallot.[1] Thousands of patients with this anomaly have experienced an amelioration of symptoms and an increase in life span as a result of this operative procedure. However, this form of surgical therapy is admittedly palliative, consisting as it does in the creation of an additional cardiovascular defect. The ultimate goal in the operative therapy of patients with the tetralogy of Fallot is correction of the basic defect, namely the valvular and/or infundibular stenosis and the ventricular septal defect. A partial realization of this goal has been accomplished by the correction of the valvular or infundibular stenosis.[2, 3, 4] This procedure has been carried out by Brock with a reasonable mortality rate and with clinical results at least as beneficial as those described following the shunt procedure.

The evolution of techniques permitting open heart surgery has further enhanced the possibility of correction of the basic defects in this anomaly. Experience with infundibular resection using open heart techniques has been limited to a small number of patients at this institution; however, definite limitations of the procedure have already been realized. Two patients are presented at this time to emphasize complications that may arise from infundibular resection in the tetralogy of Fallot when concomitant closure of the ventricular defect is not accomplished.

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CASE REPORTS

Case 1. W. H., a four year-old white boy, had been cyanotic since birth, and showed a slow weight gain and delayed growth. Cyanosis became more pronounced with the onset of walking at 10 months of age and squatting was frequent. There was a progressive limitation in exercise tolerance to one half a block. Episodes of semiconsciousness with paroxysmal dyspnea had occurred with increasing frequency since one year of age.

Physical examination revealed a small boy falling in the 10th percentile for height and weight. There was cyanosis of the lips, mucous membranes and nailbeds with clubbing of the digits. A grade 4 systolic murmur of harsh quality was audible along the left sternal border with maximum intensity in the third intercostal space.

Fluoroscopic examination showed a heart at the upper limits of normal in size with a concavity in the region of the main pulmonary artery and an uplifted cardiac apex (fig. 1A). The peripheral lung fields were abnormally clear. The aorta was increased in size and descended on the left.

The electrocardiogram showed a pattern of right ventricular hypertrophy with an R wave 27 mm. in amplitude in precordial position V_1 and an intrinsicoid deflection time of 0.04 second.

On Jan. 28, 1954 thoracotomy was performed by Dr. Henry Swan, using hypothermia and inflow occlusion. An incision was made through the infundibular chamber and a localized stenotic ring of tissue was visualized. This structure was excised and the ventricular incision closed. The postoperative course was uneventful and the patient returned home on the fifteenth postoperative day.

The exercise tolerance increased significantly and the degree of cyanosis decreased. Seven weeks postoperatively the patient developed fever and cough productive of blood streaked sputum. Physical examination revealed a visible and palpable heaving pulsation in the left second and third intercostal spaces. A grade 2 rough systolic murmur was audible along the left sternal border. The second heart sound in the left second intercostal space was increased in intensity. Fluoroscopic examination disclosed

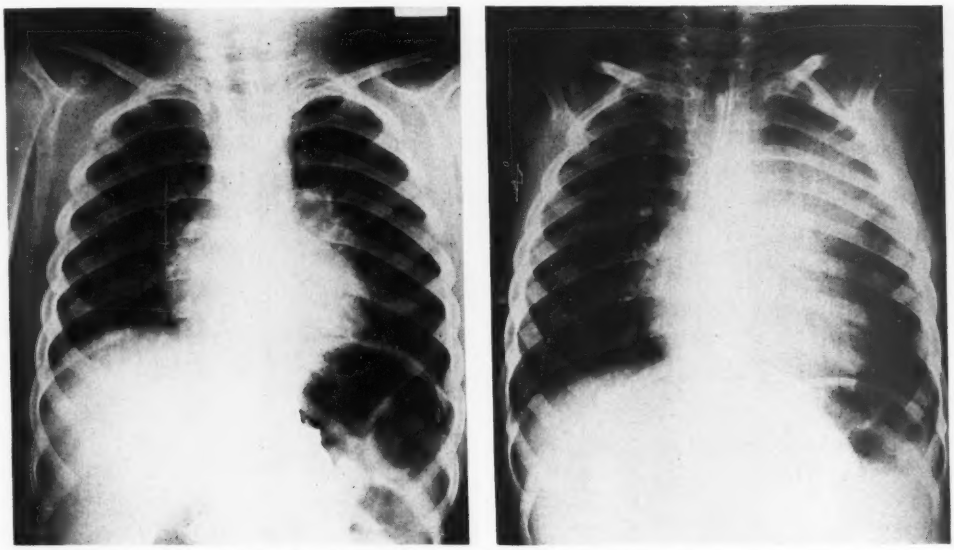

FIG. 1. The preoperative A, and postoperative B, chest roentgenogram in case 1 demonstrating the appearance of an aneurysm from the infundibular chamber.

pulsating mass in the region of the main pulmonary artery (fig. 1B). The electrocardiogram showed an inversion of previously upright T waves over the right precordial leads. The patient was hospitalized and an exploratory thoracotomy was performed on March 13, 1954. A large, thin-walled aneurysm was found arising from the infundibular chamber of the right ventricle. This was not a false aneurysm arising at the site of the previous incision in the infundibular chamber. Blood flow was occluded, and the aneurysm was opened and an endoaneurysmorrhaphy was performed with removal of the major portion of the sac. Cardiac arrest occurred with temporary reinstitution of a regular rhythm but the patient died four hours later.

Postmortem examination revealed a heart weight of 120 Gm. as compared with a body weight of 12 Kg. The right ventricle was hypertrophied, the wall measuring 9 mm. in thickness. A fibrous base was present in the area of the excised infundibular stenosis. The infundibular chamber was thin walled and showed the recent incision. The original infundibular incision was well healed. A 1.7 by 1.5 cm. ventricular septal defect was present with the aorta overriding the defect. The aorta measured 4.5 cm. in circumference while the pulmonary artery was 1.5 cm. in circumference.

Comment. The development of an aneurysm of the infundibular chamber following resection of an infundibular stenosis constitutes an unusual complication of this surgical approach to the tetralogy of Fallot. In the absence of evidence of a false aneurysm at the site of the incision or of infarction of the myocardium in this area it seems justified to suggest that this aneurysm developed as a result of the sudden increase in pressure and increase in blood flow through the previously existing infundibular chamber. At the time of the initial surgery the infundibular chamber was a thin walled structure protected from the high right ventricular systolic pressure and from a high volume of blood flow by the presence of the infundibular stenosis. Following extirpation of the infundibular stenosis this chamber was suddenly exposed to the stress of the elevated right ventricular systolic pressure and to an increased blood flow. It is likely that an element of functional valvular pulmonic stenosis complicated the hemodynamic derangement as the small pulmonic valve ring would not accommodate the increase in blood flow. The critical factor in the production of this aneurysm is considered to be the abrupt change in the hemodynamic pattern more than the magnitude of the changes in themselves. Therefore, it is proposed that the formation of the aneurysm developed as a response to this abrupt change in hemodynamics before compensatory hypertrophy of

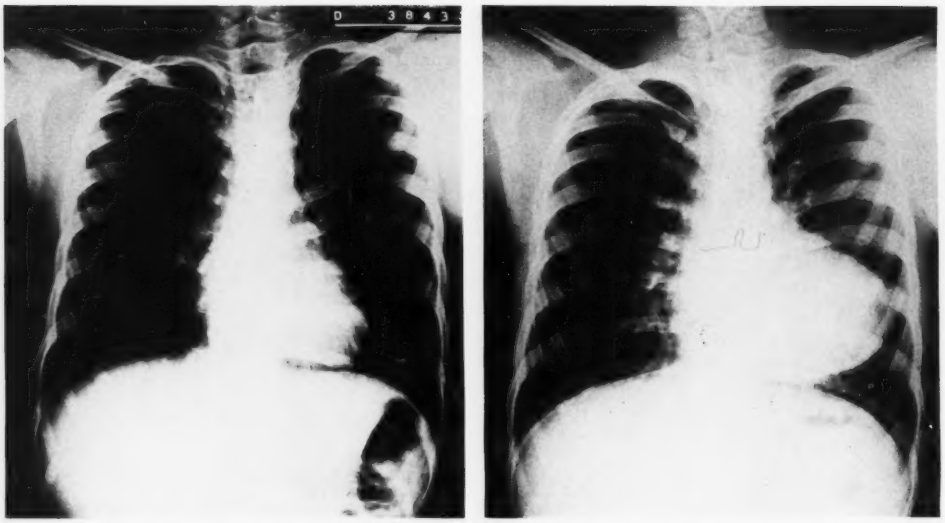

FIG. 2. The preoperative, A, and postoperative, B, chest roentgenogram in case 2 showing a considerable increase in heart size and an increase in the vascularity of the lung fields.

the myocardium in the wall of the infundibular chamber could become established.

Case 2. P. E., a 12-year-old boy, was cyanotic and presented cardiac murmurs at birth. Development was retarded with an onset of walking at 20 months of age and talking at 36 months of age. Cyanosis became more marked with the onset of walking and severe ease of fatigue, exertional dyspnea and squatting occurred. Episodes of paroxysmal dyspnea developed at 7 years of age and were associated with loss of consciousness and deep cyanosis. The patient's exercise tolerance was limited to walking one-half block prior to surgery.

Physical examination revealed cyanosis of the lips and nailbeds with severe clubbing of the digits. The heart was normal in size and no thrills or shocks were present. A harsh systolic murmur of grade 3 intensity was audible along the left sternal border with maximum intensity in the third intercostal space. The second heart sound in the second left intercostal space was normal in intensity and was pure in quality.

The fluoroscopic examination showed a decreased vascularity of the lung fields (fig. 2A). The right pulmonary artery was small and showed a reduced amplitude of pulsations. The aorta was increased in size and descended on the left. A slight concavity was present in the area of the main pulmonary artery. A small bulge was apparent high on the ventricular segment considered to represent an infundibular chamber. The cardiac apex was uplifted suggesting right ventricular hypertrophy. The electrocardiogram (fig. 3) presented a pattern suggesting right ventricular hypertrophy.

Cardiac catheterization was performed on March 16, 1953. The significant results are summarized in table 1. The catheter was introduced into the right ventricle where a pressure of 120/−3/8 mm. Hg was recorded, and was advanced into the aorta and into the pulmonary artery. The pressure tracing recorded during the withdrawal of the catheter from the pulmonary artery to the right ventricular area is shown in figure 4. An intermediate pressure is present representing an infundibular chamber. Open heart surgery was performed by Dr. Henry Swan on April 21, 1953 utilizing hypothermia and inflow occlusion. The infundibular chamber was incised and a localized diaphragm-like infundibular stenosis excised under direct vision. The infundibular orifice was increased from an initial 3 mm. diameter to an estimated 10 mm. diameter. The incision was closed and circulation re-established after a total period of eight minutes of occlusion. The postoperative course was uneventful and the patient returned home May 11, 1953.

An immediate and striking increase in exercise tolerance occurred, so that the patient was able to ride a bicycle, play baseball, walk a distance of at least a mile and was able to "keep up" with friends in all respects. Re-examination Feb. 5, 1954 revealed no cyanosis and marked regression in the degree of clubbing of the digits. The heart was enlarged to percussion, a vigorous apical thrust was visible and palpable, and a systolic thrill was present along the sternal border. A harsh systolic murmur, grade 5 in intensity, was audible along the

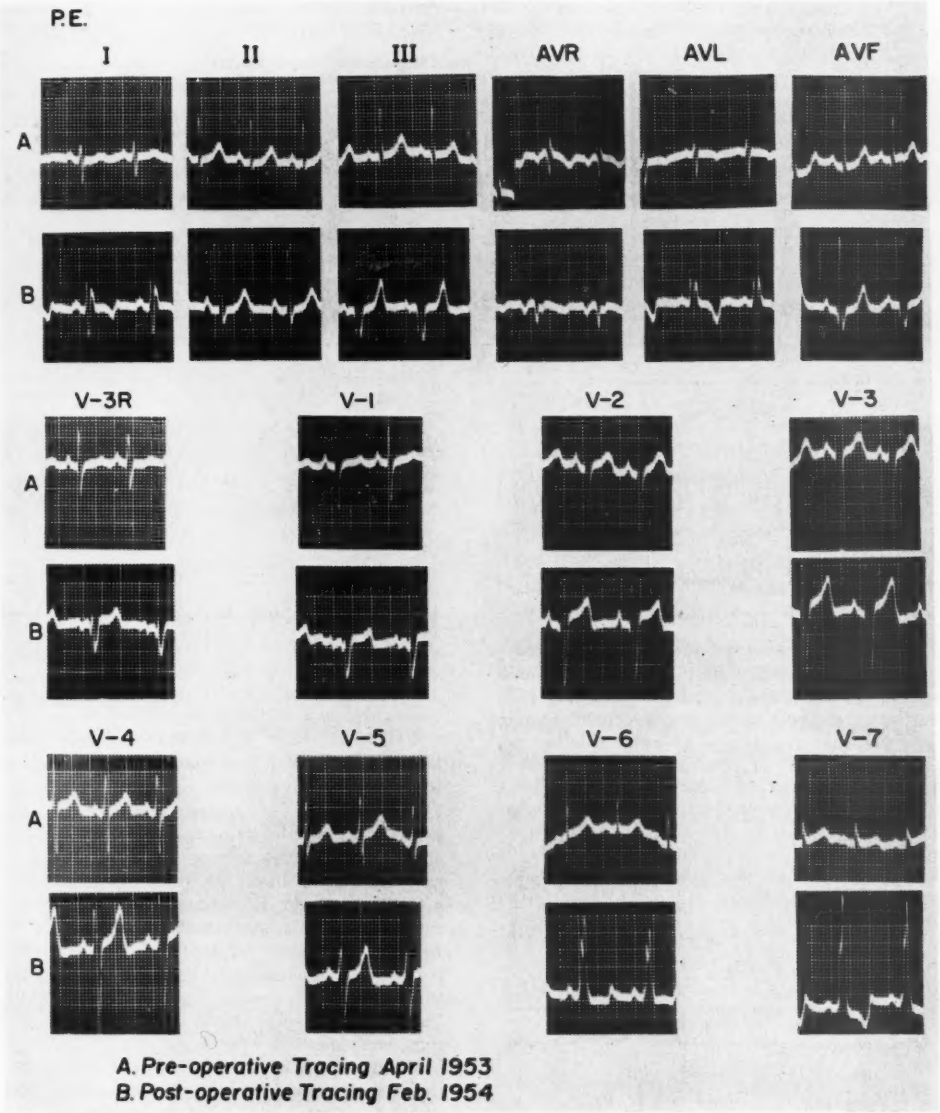

FIG. 3. The preoperative, A, and postoperative, B, electrocardiogram of case 2 demonstrating a change from a pattern of right ventricular hypertrophy to a pattern of left ventricular hypertrophy and left bundle branch block.

ft sternal border with maximum intensity in the urth intercostal space. The second heart sound in e second left interspace was increased in intensity d was finely reduplicated.

Fluoroscopic examination showed a normal scularity of the lung fields. The right pulmonary tery was small but exhibited a normal amplitude pulsation. There was a marked increase in the heart size (fig. 2 B) with a configuration suggesting left ventricular enlargement.

The electrocardiogram showed a striking change with the development of a pattern suggesting left bundle branch block with left ventricular hypertrophy (fig. 3).

Cardiac catheterization studies (table 1) demonstrated an increase in the pulmonary artery pressure

TABLE 1.—*The Pre- and Postoperative Catheterization Data Determined in Case 2*

	Hemoglobin Grams Per Cent	Pressure, mm. Hg						Blood Oxygenation, Volumes Per Cent, Per Cent Saturation							Cardiac Index, L/min./M²			Blood Shunt, L/min./M²	
		Right atrium	Right ventricle	Pulmonary artery	Infundibular chamber	Aorta	Brachial artery	Inferior vena cava	Superior vena cava	Right atrium	Right ventricle	Pulmonary artery	Aorta	Brachial artery	Systemic	Pulmonic	Effective	Right to left	Left to right
Preop., 16 March 1953	19.8	11 1	120 3	13 8	23 4	122 80	120 80	17.85 67.2	16.16 60.8	16.29 61.3	16.20 61.0		18.83 79	21.25 80.0	4.8				
Postop., 5 Feb. 1954	14.4	7 4	57 8	26 9		75 60	90 58	12.65 65.6	12.32 63.8	12.31 63.8	13.01 67.5	14.78 76.6	16.88 87.4	17.49 90.6	3.8	5.7	3.4	.4	2.3

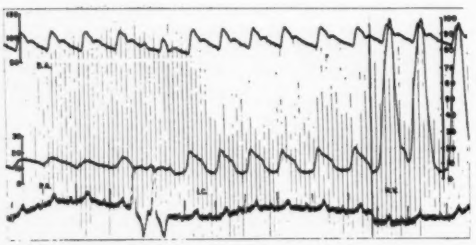

FIG. 4. The preoperative pressure tracing in case 2 showing a low pulmonary artery pressure, P.A., and intermediate infundibular chamber pressure, I.C., and a high right ventricular pressure, R.V. A short segment of the infundibular pressure tracing was removed to facilitate graphic presentation.

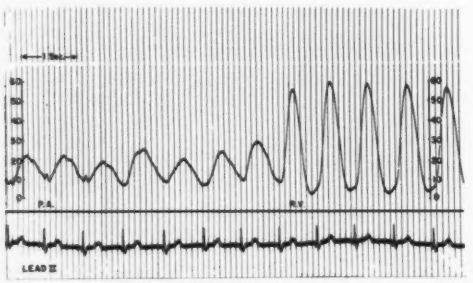

FIG. 5. The postoperative pressure tracing in case 2 showing an increase in pulmonary artery pressure, P.A., and a decrease in right ventricular pressure, R.V. There is no intermediate pressure area indicating an infundibular chamber as seen preoperatively.

to 26/9 mm. Hg with a normal contour of the pulmonary artery pressure wave. The pressure tracing obtained on withdrawal of the catheter from the pulmonary artery into the right ventricle (fig. 5) shows an abrupt transition in pressure with no intermediate pressure levels representing an infundibular chamber as noted preoperatively (fig. 4). The catheter was advanced into the aorta and a pressure of 75/60 mm. Hg determined. On withdrawing the catheter from the aorta into the right ventricle a right ventricular pressure of 57/8 mm. Hg was recorded. The continuous pressure tracing during this drawback is shown in figure 6 and demonstrates the systolic pressure gradient from the aorta to the right ventricle.

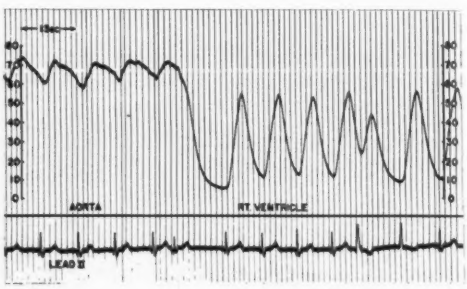

FIG. 6. The postoperative pressure tracing in case 2 on withdrawal of the catheter from the aorta into the right ventricle. A significant systolic pressure gradient is present between the aorta and right ventricle.

Re-examination in September, 1954 revealed maintenance of normal exercise tolerance. A brachial arterial oxygen saturation of 98 per cent at rest and 87 per cent following vigorous exercise was determined. Auscultation revealed the appearance of a high pitched blowing diastolic murmur in the second left intercostal space. This murmur was interpreted as indicating the development of functional pulmonic insufficiency.

Comment. The sequence of events occurring in this patient represents a second form of cardiovascular response following resection of infundibular stenosis. The infundibular resection

removed the high resistance to blood flow into the pulmonary artery and introduced into the hemodynamic pattern the relatively low resistance of the pulmonary vascular bed. The result of the removal of the obstruction to pulmonary flow was a decrease in right ventricular pressure, the establishment of a systolic pressure gradient between the left and right ventricles, and a left to right blood flow thorugh the ventricular defect. The hemodynamic pattern was therefore essentially that of an isolated large ventricular septal defect. The residual systolic pressure gradient noted postoperatively between the right ventricle and pulmonary artery (fig. 5) suggests a mild degree of valvular pulmonic stenosis, a mild degree of residual infundibular stenosis, or functional pulmonic stenosis resulting from the relatively small pulmonic valve ring. The relative lack of significance of the anatomic position of the aortic root in the hemodynamic pattern associated with a ventricular defect is well illustrated in this patient. Despite the overriding of the aorta in relation to the ventricular septal defect the right ventricular pressure was significantly less than the left (fig. 6) and the previously existing right to left shunt was completely abolished at rest as demonstrated by the full arterial oxygen saturation. It has been proposed that the presence of a ventricular defect and an overriding aorta results in an identical systolic pressure in the left and right ventricles so that infundibulectomy could not reduce the right ventricular pressure in the tetralogy of Fallot. The data presented at this time and studies on patients with isolated ventricular defects demonstrate that this view is not necessarily valid.[5] The presence of a pressure gradient between the two ventricles in patients with a ventricular defect depends upon the relative resistance offered by the pulmonary and systemic circulations and upon the size of the ventricular defect, with the position of the aortic root being of secondary importance.

Following surgery, the dominant physiologic abnormality consisted of the abrupt establishment of a left to right shunt through the ventricular defect. This was reflected dynamically by the dilatation and hypertrophy of the left ventricle, and by the increase in pulmonary blood flow with progressive dilatation of the pulmonic valve ring resulting in functional pulmonic insufficiency. The immediate clinical manifestation of these changes was a striking improvement in symptomatology exceeding that usually observed following a shunt procedure. However, the long term prognosis remains in doubt as it is anticipated that this patient will pursue the natural history of a patient with a large ventricular defect. Closure of the ventricular defect is therefore planned in this patient at such time as this operative procedure is feasible.

Discussion

The patients presented in this communication illustrate complications that may arise as a result of surgical relief of the infundibular stenosis without the concomitant closure of the ventricular defect in patients with the tetralogy of Fallot. The course in these two patients emphasizes the inherent balance of dynamic factors in this congenital anomaly. The pulmonic stenosis controls the magnitude of the left to right shunt through the ventricular defect while the ventricular defect limits the increase in right ventricular systolic pressure. One application of this concept has been the operative production of partial pulmonary occlusion in patients with large ventricular defects and high magnitude pulmonary blood flow.[6] Thus, sole correction of either the pulmonic stenosis or the ventricular defect is not a desirable definitive measure in patients with the tetralogy of Fallot. Obviously, considerable nicety of judgement is demanded at the time of surgery to determine the precise extent of infundibular resection that will result in a beneficial degree of increased pulmonary blood flow.

It is recommended, therefore, that the direct surgical approach to the pulmonic stenosis with infundibular stenosis be considered as merely an interim procedure pending the development of techniques permitting simultaneous correction of both the valvular stenosis and/or the infundibular stenosis and the ventricular defect. It is anticipated that techniques per-

mitting such procedure on a wide scale with a reasonable mortality will soon be realized.

Conclusion

Two patients with a tetralogy of Fallot are presented who demonstrate complications that may occur following infundibular resection. An aneurysm of the infundibular chamber developed in one patient and a significant left to right blood flow developed in the second patient with resulting marked enlargement of the left ventricle.

Summario in Interlingua

Es presentate duo casos pro demonstrar complicationes que pote occurrer post resection infundibular in patientes con tetralogia de Fallot. Un aneurysma del camera infundibular se disveloppava in un del patientes post le elimination del stenosis infundibular. Un fluxo ab le sinistra verso le dextera se disveloppava al nivello ventricular post le operation in un secunde patiente qui habeva un marcate allargamento cardiac e hypertrophia sinistroventricular.

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The Electrocardiographic Pattern of Right Ventricular Hypertrophy in Mitral Valve Disease

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The electrocardiograms in 32 patients with mitral valve disease have been compared with the pulmonary resistances, the pulmonary artery pressures, and the size of the mitral valve orifice. In patients with pure stenosis if the electrocardiogram showed the pattern of right ventricular hypertrophy the total pulmonary resistance was usually 1000 dynes seconds cm.$^{-5}$ or greater. If mitral insufficiency and/or aortic valve lesions were present in addition to mitral stenosis the total pulmonary resistance often exceeded 1000 dynes seconds cm.$^{-5}$ without right ventricular hypertrophy being evident in the electrocardiogram.

THE electrocardiographic pattern of right ventricular hypertrophy is frequently seen in patients with mitral stenosis. Lewis and associates[1] have pointed out that if the level of total pulmonary resistance is 1000 dynes seconds cm.$^{-5}$ or greater the electrocardiogram usually shows right ventricular hypertrophy.

Although right ventricular hypertrophy is often taken as evidence in favor of predominant mitral stenosis it is also known that this pattern can occur in patients with both mitral stenosis and insufficiency.[1]

The purpose of the present study was to investigate further the correlation of the pattern of right ventricular hypertrophy in patients with mitral valve disease with the pulmonary artery pressures, the pulmonary resistances, and the mitral valve areas.

MATERIAL AND METHODS

Thirty-nine patients with mitral valve disease have undergone cardiac catheterization in the Cardiac Laboratory at the Cincinnati General Hospital during the past three years. The present report concerns only one phase of the study. The additional physiologic measurements obtained are described in a separate communication.[2] Briefly, venous catheterization was carried out according to the method of Cournand and Ranges.[3] The resting pressures were obtained in the right auricle, right ventricle, and pulmonary artery. Pulmonary "capillary" pressures were obtained by the method described by Hellems and co-workers.[4] The pressures were recorded on a Hathaway recording oscillograph. The cardiac output was determined in the basal state according to the Fick principle. The mean "capillary," pulmonary artery, right ventricular and right auricular pressures were determined by planimetric integration.

Pulmonary arteriolar* resistance was calculated according to the formula:†

$$R = \frac{PA_m - \text{“}PC\text{”}}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

Total pulmonary resistance was calculated as follows:

$$R' = \frac{PA_m - 0}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

Mitral valve orifice areas were calculated as follows[5]:

$$MVA = \frac{MVF}{31\sqrt{\text{“}PC\text{”} - 5}}$$

Where PA_m = pulmonary arterial mean pressure in mm. Hg
$\text{“}PC\text{”}$ = pulmonary "capillary" mean pressure in mm. Hg
CO = cardiac output, cc. per second

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* "Arteriolar" is used to designate small vessels between the large pulmonary branches and the true pulmonary capillaries.

† This and the succeeding formulae have been criticized recently as not being correct.[16, 17] However, it has also been pointed out that although the results so obtained from them are crude they do serve a useful purpose in estimating the severity of augmented pulmonary or mitral valve resistances.[18] Until better formulae are devised we shall employ them, being fully aware that the results they give are not absolute but only relative.

1332 = conversion factor from mm. Hg to dynes per cm.[2]

MVF = mitral valve flow, cc. per diastolic second

$$\left(\frac{\textit{Cardiac output, cc. per min.}}{\textit{Diastolic filling period, seconds per min.}}\right)$$

5 = assumed left ventricular mean diastolic pressure, mm. Hg

31 = empirical constant.

Thirty-two of these patients had electrocardiograms consisting of the three standard leads, aV_R, aV_L, aV_F, V_1–V_6 (and V_{3R} in some) usually taken within a few days or at most a few weeks of the time of catheterization. Seventeen were thought to have pure stenosis on the basis of absent (or grade II or less) systolic mitral murmurs, no evidence of increased amplitude of the V wave in the pulmonary "capillary" pulse tracing[6, 7, 8*] or the absence of a regurgitant jet at the time of operation (13 cases).† Twelve cases were thought to have both mitral stenosis and mitral insufficiency. This was based on the presence of a grade III or more mitral systolic murmur as well as a diastolic murmur, increased amplitude of the V waves of the pulmonary "capillary" tracing[6, 7, 8], or the presence of a regurgitant jet at the time of operation (nine cases).

Three patients had combined valvular lesions. C. H. came to autopsy. He had mitral stenosis and insufficiency and aortic stenosis and insufficiency. The mitral regurgitation had been detected at the time of surgery. S. K. had mitral stenosis and aortic insufficiency (of a mild degree). H. F. had mitral stenosis and insufficiency and aortic stenosis.

The criteria used for right ventricular hypertrophy[9, 10, 11, 12] were those of a qR pattern in V_{3R} or V_1, an R wave in V_1 of 7 mm. or greater, an R/S ratio in V_1 greater than 1, or a delay in the onset of the intrinsicoid deflection in V_1 of from 0.035 to 0.05 second. Incomplete right bundle branch block[9, 13] was diagnosed on the basis of an rSR′ pattern in V_{3R} or V_1 with delay in the onset of the intrinsicoid deflection of R′ from between 0.05 and 0.075 second. If the height of R′ exceeded 10 mm. it was taken as evidence of right ventricular hypertrophy in addition to incomplete right bundle branch block.[13] The P waves in the standard leads were considered to be abnormal if they were 0.12 second or greater in duration or 3 mm. or more in height, or were notched.[14] Heart position was classified according to the criteria of Wilson.[10]

The patterns encountered in these 32 patients were compared with the resting pulmonary artery pressures (systolic and diastolic, and mean), with the pulmonary arteriolar resistance, with the total pulmonary vascular resistance, and with the mitral valve area.

Results

Pure Mitral Stenosis (table 1)

Seventeen patients had pure mitral stenosis. The total pulmonary vascular resistance ranged from 608 to 4411 dynes seconds cm.$^{-5}$ Nine cases showed the pattern of right ventricular hypertrophy, all except one having a total pulmonary vascular resistance exceeding 1000 dynes seconds cm.$^{-5}$ and averaging 1822 dynes seconds cm.$^{-5}$.* Two cases exhibited incomplete right bundle branch block, one with a total pulmonary vascular resistance of 1163 and one with a resistance of 608 dynes seconds cm.$^{-5}$.

Six cases presented no evidence of right ventricular hypertrophy or bundle branch block. The total pulmonary vascular resistance was less than 1000 dynes seconds cm.$^{-5}$ in all, averaging 754 dynes seconds cm.$^{-5}$.

The mean pulmonary artery pressure ranged from 41 to 90 mm. Hg, averaging 61 mm. Hg for the nine patients with right ventricular hypertrophy, 49 mm. Hg for the two with incomplete right bundle branch block, and 50 mm. Hg for the remaining six cases.

Four patients had auricular fibrillation. Of the 13 with sinus rhythm, twelve had abnormal P waves.

Sixteen of the 17 patients in whom the valve area was either estimated at operation or was calculated were found to have orifices of 1.0 cm.^{2} or less. Four of the nine patients who had the pattern of right ventricular hypertrophy had mitral valve areas of 0.5 cm.^{2} or less.

Mitral Stenosis and Insufficiency (table 2)

Twelve patients had both mitral stenosis and insufficiency. The total pulmonary vascular resistance was measured in 11 and was found to range from 471 to 2384 dynes seconds cm.$^{-5}$

Four of the five cases who showed the pattern

* We are no longer considering increased amplitude of the V wave as a reliable sign of mitral insufficiency.

† The absence of a regurgitant jet at the time of surgery is probably the best available objective means of diagnosing pure mitral stenosis.

* One of these nine cases (D. M.) showed a voltage of 23 mm. in aV_F; this was interpreted as probably representing left ventricular hypertrophy although the cause for this was not apparent (no mitral insufficiency, aortic valve lesions, or systemic hypertension).

TABLE 1.—*Pure Mitral Stenosis*

Patient.	Rhythm	Pressures (mm. Hg)				Resistances (dynes sec. cm.$^{-5}$)		Area Mitral Valve (cm^2)	Electrocardiogram						
		RA	"PC"	PA		Pulmonary Arteriolar	Total Pulmonary		Abnormal P Waves			RVH	IRBBB	LVH	Position
				S/D	Mean				Broad	Tall	Notched				
B. P.	A. F.	22	—	134–158 / 58–72	90	1758*	2813	<0.5†	−	−	−	+	0	0	V
J. F.	Sinus	15	25	132/50	85	3114	4411	<0.5†	+	+	+	+	0	0	V
M. E.	A. F.	15	—	74–100 / 40–60	59	609*	1497	0.9†	−	−	−	+	0	0	SV
M. H.	Sinus	9	—	80/30	42	443*	1033	0.4†	+	0	0	+	0	0	V
H. S.	Sinus	8	22	68/46	51	368	648	1.4	+	0	+	+	0	0	Ind.
J. Pi.	Sinus	2	26	84/48	60	897	1583	0.8	0	0	0	+	0	0	V
I. E.	Sinus	5	24	80/30	42	443	1033	0.6†	+	0	0	+	0	0	V
D. M.	Sinus	2	—	85/25	52	425*	1299	0.8†	0	0	+	+	0	+	V
W. F.	Sinus	24	23	102/44	65	1795	2278	0.4†	+	+	0	+	0	0	V
M. S.	A. F.	4	23	70/35	54	668	1163	0.7†	−	−	−	0	+	0	I
I. K.	Sinus	7	—	70/35	43	110*	608	1.0	+	0	+	0	+	0	V
S. K.	Sinus	6	—	60/30	41	99*	674	0.7†	+	0	+	0	0	0	SV
J. P.	Sinus	3	—	74/36	51	204*	650	0.5†	0	0	+	0	0	0	V
G. W.	Sinus	9	27	62/33	42	311	889	<0.5†	0	+	0	0	0	0	V
S. M.	Sinus	—	—	98/52	78	—	775	0.7†	+	0	+	0	0	0	I
H. B.	A. F.	5	27	54/26	43	293	786	0.8	−	−	−	0	0	0	SV
A. T.	Sinus	—	17	54/32	42	447	751	0.3†	+	0	+	0	0	0	SV

RA: Right auricular, PC: Pulmonary capillary; RVH: Right ventricular hypertrophy; IRBBB: Incomplete right bundle branch block; LVH: Left ventricular hypertrophy; V: Vertical; SV: Semivertical; I: Intermediate; Ind: Indeterminate.

* = Minimal pulmonary arteriolar resistance, calculated on an assumed pulmonary capillary pressure of 35 mm. Hg.

† = Size of mitral valve orifice estimated at time of surgery.

TABLE 2.—*Mitral Stenosis and Mitral Insufficiency**

Patient	Rhythm	Pressures (mm. Hg)				Resistances (dynes sec. cm.$^{-5}$)		Forward Area Mitral Valve (cm^2)	Electrocardiogram						
		RA	"PC"	PA		Pulmonary Arteriolar	Total Pulmonary		Abnormal P Waves			RVH	IRBBB	LVH	Position
				S/D	Mean				Broad	Tall	Notched				
F. J.	A. F.	18	23	78/43	59	773	1285	1.2	−	−	−	+	0	0	V
R. U.	A. F.	11	36	68/34	43	128	779	2.0	−	−	−	+	+	0	V
F. R.†	Sinus	13	—	122/64	88	1436*	2384	0.8	0	+	0	+	0	0	V
W. S.†	Sinus	—	44	142/76	97	999	1828	0.8	0	0	+	+	0	0	V
P. L.†	Sinus	3	26	92/44	65	861	1435	0.9	+	0	0	+	0	0	SV
S. C.	A. F.	—	38	72/46	64	378	935	—	−	−	−	0	+	0	I
J. K.	Sinus	4	28	56/35	43	132	482	1.1	+	0	0	0	0	0	V
G. B.	Sinus	9	27	44/32	—	—	—	—	0	0	0	0	0	0	SV
E. McC.	A. F.	7	41	98/52	78	668	1407	0.6	−	−	−	0	0	0	V
V. H.	A. F.	14	—	80/11	50	641*	1466	0.9	−	−	−	0	+	0	V
D. F.	Sinus	13	26 to 36	62/35	49	221	471	—	0	0	0	0	0	+	SV
B. B.	Sinus	18	—	102/68	81	1058*	1861	0.4	0	0	0	0	0	0	V

* Same as table 1 with following additions: Forward area of mitral valve: estimation of size of orifice of mitral valve at time of surgery.

† Regurgitant jet very small at time of surgery.

TABLE 3.—*Mitral and Aortic Valve Lesions*

Patient	Rhythm	Pressures (mm. Hg)				Resistances (dynes sec. cm.$^{-5}$)		Forward Area Mitral Valve (cm^2)	Electrocardiogram						
		RA	"PC"	PA		Pulmonary Arteriolar	Total Pulmonary		Abnormal P Waves			RVH	IRBBB	LVH	Position
				S/D	Mean				Broad	Tall	Notched				
I. R. (AI, MS)	Sinus	0.3	19	45/8	29	205	594	1.0	0	+	+	0	0	0	V
C. H. (MS, MI, AS, AI)	A. F.	19	45	102/64	75	766	1915	1.1	−	−	−	0	0	0	SV
H. F. (MS, MI, AS)	A. F.	16	33	150/85	100	2898	5033	—	−	−	−	0	0	0	SV

Legend: Same as table 1 with following additions: MS: Mitral stenosis; MI: Mitral insufficiency; AS: Aortic stenosis; AI: Aortic insufficiency.

of right ventricular hypertrophy had a total pulmonary vascular resistance of greater than 1000 dynes seconds cm.$^{-5}$, averaging 1542 dynes seconds cm.$^{-5}$. One case (R. U.) had both right ventricular hypertrophy and incomplete right bundle branch block, with a total pulmonary vascular resistance of 779 dynes seconds cm.$^{-5}$.

Two patients (S. C. and V. H.) who had incomplete right bundle branch block had total pulmonary vascular resistances of 935 and 1466 dynes seconds cm.$^{-5}$ respectively.

Two patients (E. McC. and B. B.) with resistances of 1407 and 1861 dynes seconds cm.$^{-5}$ showed neither right ventricular hypertrophy nor right bundle branch block. One case (D. F.) showed increased voltage and delay in the onset of the intrinsicoid deflection in leads over the left ventricle; these changes were thought to be consistent with left ventricular hypertrophy.[15]

The mean pulmonary artery pressure ranged from 43 to 97 mm. Hg with an average of 70 for the five patients with right ventricular hypertrophy, 67 for the two with incomplete right bundle branch block, and 63 for the remaining five patients.

Five patients showed auricular fibrillation. Of the seven who showed sinus rhythm, four had abnormal P waves.

The mitral valve area was measured at surgery in nine patients. It was found to range from 0.4 to 2.0 cm.^{2}.

Mitral and Aortic Valve Disease (table 3)

Three patients had mitral and aortic valve disease. The total pulmonary vascular resistance ranged from 594 to 5033 dynes seconds cm.$^{-5}$ with an average of 2514. None of these cases showed either right ventricular hypertrophy or right bundle branch block.

The mean pulmonary artery pressure ranged from 29 to 100 mm. Hg with an average of 68.

Two cases had auricular fibrillation and the one with sinus rhythm had abnormal P waves.

The mitral valve area was measured at surgery in two patients, being 1 cm.^{2} in one case and 1.1 cm.^{2} in the second.

DISCUSSION

Our findings in cases of pure mitral stenosis are essentially in agreement with those of Lewis and his group.[1] If the total pulmonary resistance (which is a function of both pulmonary arteriolar resistance and mitral valve area) is 1000 dynes seconds cm.$^{-5}$ or greater then the pattern of right ventricular hypertrophy or incomplete right bundle branch block is usually (but not invariably) present.

On the other hand we found that if in addition to mitral stenosis, mitral insufficiency and/or aortic valve lesions exist, total pulmonary resistance may well exceed 1000 dynes seconds cm.$^{-5}$ without the pattern of right ventricular hypertrophy or incomplete right

bundle branch block being present. In other words, in lesions which will cause strain on the left ventricle, even though the total pulmonary resistance is greater than 1000 dynes seconds cm.$^{-5}$, the pattern of right ventricular hypertrophy may not be present.

Johnson and associates[9] found in their patients with cor pulmonale secondary to chronic lung disease that if the pattern of right ventricular hypertrophy occurred the pulmonary artery mean pressure almost always exceeded 30 mm. Hg. Our findings in cases of mitral stenosis are in agreement with this. On the other hand, like Johnson and associates,[9] we also had a number of patients (12 in our study) in whom the mean pulmonary artery pressure exceeded 30 mm. Hg who did not show either right ventricular hypertrophy or incomplete right bundle branch block.

Only four of the 32 patients studied failed to show either auricular fibrillation or abnormal P waves. Most of our cases had rather severe mitral stenosis. This high incidence of auricular abnormalities may not be found in patients with lesser degrees of stenosis.

The pulmonary "capillary" pressure (presumably a reflection of left auricular pressure) was found to be elevated, as would be expected, in all patients in whom it was measured.

Eight of the nine patients with pure stenosis who had the pattern of right ventricular hypertrophy had mitral valve areas less than 1.0 cm.^{2}. The total pulmonary resistance which is a measure of the resistance of the narrowed pulmonary arterioles (pulmonary arteriolar resistance) and the stenosed mitral valve[1] was greater than 1000 dynes seconds cm.$^{-5}$ in eight of the nine cases. The single exception was one patient (H. S.) who had a valve area of 1.4 cm.^{2} and a total pulmonary vascular resistance of 648 dynes seconds cm.$^{-5}$.

On the contrary two patients (G. W., A. T.) with valve areas of less than 0.5 cm.^{2} and total pulmonary vascular resistances of 889 and 751 dynes seconds cm.$^{-5}$, respectively, failed to show right ventricular hypertrophy. This is in accord with the concept of Lewis and coworkers[1] that the electrocardiographic changes diagnostic of right ventricular hypertrophy are a function of both mitral valve area and pulmonary arteriolar resistance. Thus, although the mitral valve was tight in both patients, the pulmonary arteriolar resistances (311 and 447 dynes seconds cm.$^{-5}$, respectively) were not markedly increased so that the total pulmonary resistance did not reach the critical level of 1000 dynes seconds cm.$^{-5}$ above which the pattern of right ventricular hypertrophy usually develops in pure mitral stenosis.

Summary

The electrocardiographic patterns encountered in 32 patients with mitral valve disease were compared with the resting pulmonary artery pressures, with the pulmonary resistances and with the mitral valve areas.

Seventeen patients had pure mitral stenosis. Nine of these showed the pattern of right ventricular hypertrophy and two showed incomplete right bundle branch block. Eight of the nine with hypertrophy and one with incomplete right bundle branch block had total pulmonary resistances in excess of 1000 dynes seconds cm.$^{-5}$.

In pure mitral stenosis if the total pulmonary resistance is 1000 dynes seconds cm.$^{-5}$ or greater the electrocardiogram will usually (although not invariably) show the pattern of either right ventricular hypertrophy or incomplete right bundle branch block.

If mitral insufficiency and/or aortic valve lesions co-exist with mitral stenosis, the total pulmonary resistance may exceed the level of 1000 dynes seconds cm.$^{-5}$ many times without the development of the pattern of right ventricular hypertrophy.

When the electrocardiographic pattern of right ventricular hypertrophy is encountered in mitral valve disease the following inferences may be drawn:

a. The patient does not necessarily have pure mitral stenosis although it is probably the predominant lesion.
b. The total pulmonary resistance is probably 1000 dynes seconds cm.$^{-5}$ or greater.

Summario in Interlingua

In 32 patientes de morbo del valvula mitral, comparationes esseva executate inter le configurationes electrocardiographic e le valores

obtenite in mesurationes del resistentias pulmonar, del pressiones del arteria pulmonar, e del dimensiones del orificio del valvula mitral. In patientes con pur stenosis, le presentia de configurationes de hypertrophia dexteroventricular in le electrocardiogramma correspondeva generalmente a resistentias pulmonar total de 1000 dyna-sec-cm^{5} o plus. Si ultra stenosis mitral le patiente habeva insufficientia mitral e/o lesiones del valvula aortic, le resistentia pulmonar total frequentemente excedeva 1000 dyna-sec-cm^{-5} sin evidentia de hypertrophia dexteroventricular in le electrocardiogramma.

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A Two-Dimensional Ballistocardiographic Study of 59 Apparently Normal Persons

An Analysis of the IJ Segment as it Relates to Body Surface Area and the Anatomic Position of the Heart

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Simultaneous longitudinal and transverse ballistocardiograms were obtained from 59 apparently normal persons. A highly significant correlation was found to exist between body surface area and basal longitudinal "IJ" amplitude. The significance of this is discussed. The transverse IJ amplitude is shown to be related to the rotation of the heart about the anteroposterior axis of the body.

THE formulas which have been devised to determine cardiac output by means of the ballistocardiogram assume that the stroke volume is roughly proportional to the amplitude of the IJ segment. This is probably true in normal subjects, for there exists a good correlation between cardiac output as determined by the ballistocardiogram and the ethyl iodide and direct Fick (catheter) methods.[1, 2, 3, 4] However, considerable doubt exists as to the value of the ballistocardiogram as a measure of cardiac output. Taylor and Tiede[5] concluded that the high-frequency ballistocardiogram is measuring something only indirectly related to the cardiac output. The results of their study indicated that the instrument gives estimates of cardiac output which for all practical purposes are unrelated to body size. That is, the high-frequency ballistocardiogram gives cardiac outputs which do not distinguish between large and small individuals. The low-frequency, critically damped ballistocardiograph, acetylene method, corrected acetylene method, and direct Fick method, all distinguish between large and small individuals in a satisfactory manner. These methods give cardiac outputs which are related to body surface area.[5]

One of the purposes of this study was to explore the correlation of the IJ amplitude of the high-frequency ballistocardiogram with body surface area in order to investigate the feasibility of developing more accurate formulas for the prediction of cardiac output. We were also interested in learning what effect, if any, the anatomic position of the heart might have on the "IJ" segment. Transverse displacement ballistocardiograms were included in this study in order to study that portion of the transverse record which corresponds in time to the IJ segment of the longitudinal ballistocardiogram. Our attention has been focused on the IJ segment because it is one of the most conspicuous portions of the ballistocardiogram, the I and J waves occur during early systole and are used in the formulas for determining cardiac output and the amplitudes of these waves are commonly reduced in abnormal records.

The ballistocardiograms in this study were taken from a high-frequency ballistic table with two degrees of freedom. The displacement of the table in the head-to-foot and side-to-side directions is measured by means of Statham strain gages. The output of the strain gage bridge circuit is amplified and recorded by pen motors, which permit simultaneous recording of the longitudinal and transverse displacements, together with the electrocardiogram. The transverse recordings are obtained from the head end of the table where the movement

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of the table is greatest. The design of the table has been described elsewhere.[6]

Material

Fifty-nine normal subjects were included in this study. In order to study a portion of the group in greater detail, the first 18 subjects were considered separately. Four women and 14 men were selected from the staff of the Cincinnati General Hospital. Their ages ranged from 24 to 44 years. All were asymptomatic and apparently in good health. The size and configuration of their hearts were normal as determined by x-ray films. Twelve-lead electrocardiograms were taken on each subject and were also normal.

The second group consisted of 21 healthy male medical students and 20 patients from the male surgical ward of the Cincinnati General Hospital. The 20 patients had been admitted for elective surgical procedures such as herniorraphies and excision of keloids, and all were considered to be free of cardiac or vascular disease. This group ranged in age from 20 to 30 years.

Method

Ballistocardiograms were obtained from the 59 normal subjects. The tracings were taken three and one-half to four hours following the subject's last meal, and after the subject had rested on the table for 15 minutes. The subjects who smoked were asked to refrain from smoking for at least one hour prior to the test. These tracings were considered to be basal ballistocardiograms. The IJ segment amplitude was determined in the second group of 41 subjects by finding the average longitudinal IJ amplitude in three consecutive respiratory cycles. This consisted of 9 to 22 measurements for each record.

Body size was determined by the DuBois surface area formula, for it provides a good estimate of the body size factor. It has been shown for men to correlate with the size factor estimate to the extent of 0.98.[7, 8] The first group of subjects was studied in greater detail:

Test Meal

To study the orientation of the IJ segment in the frontal plane of the body as it relates to the anatomic position of the heart, a form of "exercise" was desired which would alter the direction of the frontal plane IJ segment as compared with the basal state. The result of the "exercise" should be an increased "cardiac force" without an associated tachycardia or dyspnea, thereby eliminating increased movements of the chest wall or abdomen due to respiration. A simple test meal was selected which consisted of 500 cc. of chocolate milk and four graham crackers, containing a total of 630 calories. After the basal ballistocardiogram wa recorded, the test meal was consumed, and the subject rested on the table until after the second tracing was taken, 10 minutes later. To standardize the test, certain preliminary studies were performed. The first study was to record continuous half-hour ballistocardiograms following the test meal to determine the optimum time at which the second tracing should be taken. The greatest change in amplitude of the ballistic waves, particularly the IJ segment, was noted at about 10 minutes. The effect on the ballistocardiogram of the coldness of the milk and the volume of fluid in the stomach was next studied, for it seemed possible that the changes in amplitude might be caused in part by the elevation of the diaphragm by the stomach. This did not prove to be the case. When 500 cc. of ice water were consumed, the amplitudes of the ballistic waves were the same as the basal tracing at the end of two minutes and remained so throughout the 15 minutes the tracing was taken. It was concluded that the probable effect of the test meal was to produce a splanchnic dilatation with a resultant increase in cardiac output. The test meal was considered a satisfactory form of "exercise" and was used in this study as outlined above.

The average "cardiac force", as measured from five consecutive respiratory cycles, was computed for the basal longitudinal and transverse ballistocardiograms and the ballistocardiograms taken 10 minutes after the test meal. "Cardiac force" is an expression developed by Starr[9] and is the sum of the largest I and J vertical height and the smallest I and J vertical height. The measurements for calculating "cardiac force" from the transverse record were obtained by measuring the amplitude of the waves which corresponded in time to the IJ segments of the longitudinal record. The longitudinal "cardiac force" was plotted on the ordinate, and the transverse "cardiac force" was plotted on the abscissa. The resultant or effective "cardiac force" was plotted as a vector which represented projections of the IJ segment in the frontal plane of the body. For lack of a better term, we shall refer to this vector as the frontal plane IJ segment. Following the ingestion of food, the change in magnitude and direction of the frontal plane IJ segment was measured. The change in direction was considered negative if it became more vertical by comparison with the basal tracing, or positive if it moved towards the horizontal. This change was also measured in degrees.

It should be noted that in both groups IJ amplitude was measured which eliminated the selection of a baseline as required in determining I and J wave amplitudes. The correct selection of a baseline is critical for an error of 1 mm. may make considerable difference in the results. Measurements of IJ amplitude were read to the nearest half millimeter.

TABLE 1.—*Roentgenographic and Ballistocardiographic Data Obtained From the Subjects of Group 1*

Subject: Age, Sex	$\frac{Tr.L}{Tr.L. + Tr.R.} \times 100$	Basal "Cardiac Force" (mm)			Percent Change in "C.F." After Food Intake			Frontal Plane IJ		Body Surface Area (M^2)
		Long.	Trans.	Frontal Plane IJ	Long.	Trans.	Frontal Plane IJ	Basal Direction	Degree* Change	
1. B.K. 44 M	74%	25.6	4.5	26.2	−5%	−17%	−6%	10.0°	−1.3°	1.87
2. W.K. 26 M	63	42.9	10.8	44.3	−6	−38	−8	14.0	−4.9	2.08
3. H.P. 29 M	64	27.5	7.5	28.5	−15	+17	−13	15.3	+5.4	1.97
4. R.E. 31 M	69	29.6	9.3	30.9	+20	−46	+16	17.2	−9.2	2.00
5. W.S. 34 M	72	38.7	7.3	39.3	−7	+71	−3	10.5	+8.5	1.82
6. M.K. 30 F	59	21.2	5.3	21.7	+3	−13	+3	14.1	−2.3	1.80
7. J.M. 37 M	67	28.1	7.8	29.2	+11	−47	+8	15.5	−8.1	1.95
8. I.W. 27 M	66	23.4	2.9	23.5	+12	−24	+12	7.1	−2.1	1.92
9. M.L. 29 F	65	30.2	12.8	32.8	+16	−27	+11	23.0	−8.2	1.77
10. J.H. 29 M	56	29.7	6.6	30.4	−9	−68	−11	12.6	−7.8	1.80
11. J.Z. 30 M	74	31.3	6.2	31.9	+11	+21	+11	11.1	+1.4	2.01
12. D.B. 25 M	65	28.9	2.6	29.1	+103	0	+103	5.2	−2.7	2.06
13. H.R. 37 F	65	18.0	5.6	18.8	+32	−21	+28	8.2	−3.4	1.59
14. A.H. 30 M	71	45.1	4.0	44.8	+5	+48	+6	5.1	+2.1	2.09
15. R.H. 24 M	69	31.8	14.0	34.8	−6	0	−7	23.3	+2.5	2.15
16. W.C. 27 M	70	39.4	7.5	40.2	+14	+64	+16	10.8	+4.4	2.04
17. A.E. 27 M	77	23.9	3.6	24.3	−11	+69	−9	8.3	+7.6	1.91
18. Z.T. 26 F	69	16.1	6.3	17.3	+2	−84	−5	21.1	−17.9	1.57
									Mean =	1.91
									S.D. =	.16

* + = moves from the vertical.
− = moves toward the vertical.

Anatomic Position of the Heart

The heart may rotate about three anatomic axes: the anteroposterior axis, becoming horizontal or vertical in position; the longitudinal axis, rotating clockwise or counterclockwise; and the transverse axis, moving the apex anterior or posterior. In this study, we were concerned only with the anteroposterior axis. Anteroposterior teleoroentgenograms were taken at 6-foot target-film distance with the patient in the supine position.

There are no suitable standards for comparison of the rotation of the heart about the anteroposterior axis as chest x-ray films generally are not taken in the supine position, and most roentgenographic measurements are concerned with cardiac size rather than with cardiac position. Measurements were made which utilized transverse diameters, frontal cardiac area and the angle formed by the longitudinal diameter* with the horizontal. The latter two methods were discarded, for they seemed to be less precise than the measurement of transverse diameters, primarily because of the error in determining the upper or lower borders. Planimetric determination of the cardiac area is also less precise than is a linear measurement.

The transverse diameter is defined as the sum of the maximum projections to the right and left heart borders from the midline. The following formula was used to determine the anatomic position of the heart:

$$\frac{Tr.\ L}{Tr.\ L + Tr.\ R} \times 100$$

where *Tr. L* = maximum projection to the left heart border from the midline, and *Tr. R* = maximum projection to the right heart border from the midline.

Since *Tr. L.* is always greater than *Tr. R*, it should be noted that the formula for determining the anatomic position of the heart is also a measure of the asymmetry of the organ projected on the frontal plane of the body.

No attempt was made to classify the heart position as vertical or horizontal, but rather the resultant percentage of the above formula was used in the determination of correlation coefficients. However, the inference is made that the larger the percentage of the heart to the left of the midline, the greater the counter-clockwise rotation of the heart about the anteroposterior axis with a resultant horizontal position of the heart.

* A line which extends from the junction of the cardiac silhouette and vascular pedicle on the right to the junction of the apex and diaphragm on the left.

TABLE 2.—*Data Obtained from the Subjects of Group 2*

Subject	Age	Blood Pressure	Pulse	B.S.A. (M^2)	Height (in.)	Weight (lb.)	Basal Long. IJ Amplitude
1. G.S.	24	106/70	55	2.04	73	180	21.8
2. R.K.	23	110/72	90	1.76	69.5	138	14.4
3. R.P.	23	110/70	80	1.69	64	145	9.2
4. C.B.	21	116/68	50	1.66	67	130	12.9
5. S.R.	20	130/100	53	2.00	73	173	11.0
6. C.B.	20	115/90	62	1.58	64.5	121.5	7.3
7. J.A.	21	123/84	68	1.81	67	157	15.1
8. F.R.	21	120/80	68	1.75	67	145	15.4
9. J.D.	29	125/80	74	1.72	64.5	148	9.8
10. R.C.	27	110/70	72	1.77	67	150	12.8
11. D.S.	22	120/80	76	2.00	73	172	16.1
12. C.W.	21	120/76	67	1.76	69	144	12.8
13. E.B.	27	130/88	75	1.87	68	167	8.3
14. T.H.	22	110/70	68	1.71	68.5	132	13.0
15. R.R.	30	108/72	65	1.90	73	152	17.2
16. F.B.	20	118/74	62	1.70	69	130	8.4
17. M.E.	25	110/60	57	1.83	66.5	163	13.7
18. W.S.	21	130/78	74	1.88	70.5	158	14.6
19. F.O.	22	110/70	56	1.82	73	138	18.3
20. T.A.	27	130/70	73	1.97	71	175	20.6
21. S.S.	25	116/78	87	1.77	67.5	147	18.3
22. J.H.	22	122/76	65	1.88	69	163	14.5
23. H.B.	24	124/82	69	1.92	68.5	170	17.5
24. D.D.	24	104/70	69	1.74	66	147	14.9
25. R.G.	26	116/74	55	1.90	69	166	17.1
26. D.H.	24	130/90	64	2.08	71	197	14.7
27. J.S.	25	132/82	63	1.77	66.5	151	14.0
28. A.C.	27	112/74	62	1.94	69.5	175	18.1
29. R.G.	25	122/82	62	2.32	75	230	20.6
30. A.W.	22	102/64	52	1.68	69	170.5	15.1
31. R.J.	25	114/76	64	1.94	69.75	172.5	20.5
32. E.S.	25	110/70	64	1.84	69	154	15.5
33. R.B.	26	108/68	58	1.88	70.75	156	20.0
34. H.P.	28	116/78	74	1.99	72	173	14.8
35. R.S.	25	116/76	77	1.84	68	158	15.9
36. M.S.	24	108/62	84	1.75	68.5	140	23.2
37. J.H.	27	116/66	50	1.96	70.5	175	20.2
38. H.F.	23	115/70	68	1.77	66.5	150	13.5
39. S.H.	24	118/78	76	2.04	71.5	187	21.1
40. J.G.	23	120/74	62	1.81	67	157	14.2
41. P.F.	27	117/70	72	1.88	69.5	158	21.8

Mean = 1.85
S.D. = .14

RESULTS

The results of this study are tabulated for the first group of 18 normal subjects in table 1, and for the second group of 41 normal subjects, in table 2. It will be noted in table 3 that a highly significant correlation exists between body surface area and basal longitudinal IJ amplitude. The percentage increase in magnitude of the transverse "IJ" segment, following the ingestion of food, correlates significantly with rotation of the heart about the anteroposterior axis of the body. Ballistocardiograms obtained from a subject in this study are reproduced in Figures 1a and 1b.

DISCUSSION

The results of Scarborough's[10] ballistocardiographic study of 165 normal men and 77 normal women demonstrated that the IJ amplitude (inspiratory, expiratory and mean) is significantly smaller in women than in men. It has been assumed that the differences in IJ amplitude between the two sexes are largely due to differences in body size. In Scarborough's normal group, there was no significant correlation between IJ amplitude and body surface area in either the men alone or the women alone. However, when the data from men and women were combined, a significant correlation resulted. It is certainly true that if a correlation coefficient is to have meaning, both variables should be normally distributed. Using data supplied by Isaac Starr from a group of 100 subjects, Scarborough obtained results very similar to those of his own group and concluded that surface area has little influence on IJ amplitude. In a study such as this, it is important that basal ballistocardiograms be recorded. In Scarborough's study, no attempt was made to secure records in the postabsorptive period only.

The results of our study of 41 normal males indicate that the relationship of body surface area to basal longitudinal IJ height is a close one. The group of four normal women and 14 normal men demonstrated a close relationship between body surface area and the heart's force. The basal longitudinal IJ height, as recorded by the high-frequency ballistocardiograph, distinguishes between large and small individuals. It is our hope that a more accurate formula for cardiac output can be devised and later tested by comparison with outputs calculated by the Fick principle. Body length cor-

TABLE 3.—*Correlation Coefficients*

Group 1	Basal "Cardiac Force"			Percent Change in "C.F." after Food Intake			Frontal Plane IJ	
	Long.	Trans.	Frontal Plane	Long.	Trans.	Frontal Plane	Basal Direction	Degree Change
I. Rotation of heart about A-P Axis	.054	−.149	.043	−.111	.558*	−.085	−.179	.408
II. Body surface area	.683†	.172	.395					

Group 2	B.S.A.	Ht.	Wt.
Basal Long. IJ Amplitude	.543‡	.542‡	.460†

* $0.02 < p > 0.01$.
† $0.01 < p > 0.001$.
‡ $p < 0.001$.

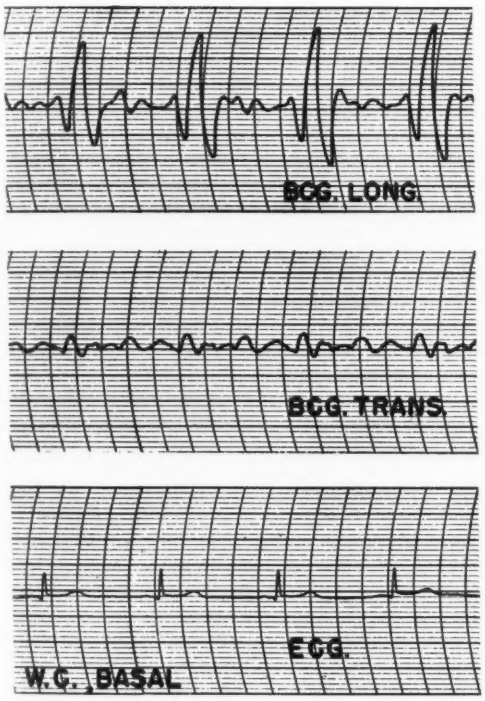

FIG. 1a. W. C., a 27 year old healthy male with a horizontal heart. The left transverse diameter obtained from the chest x-ray film is equal to 70 per cent of the transverse diameter. The QRS axis of the electrocardiogram is equal to +15 degrees. Figure 1a is the basal ballistocardiogram.

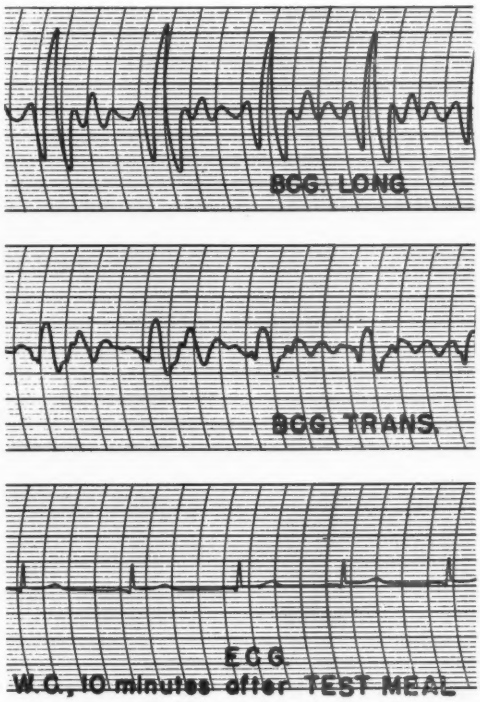

FIG. 1b is the ballistocardiogram taken 10 minutes after the ingestion of food. Note the increase in ballistic amplitude of the transverse displacement record following the ingestion of food.

relates as well with basal IJ amplitude as does body surface area, as r = respectively, .542 and .543 ($p < 0.001$). Perhaps body length should be included in the formula for cardiac output.

Possibly body length influences the amplitude and form of the I and J waves, for the length of the vessels will be proportional to the length of the body. Starr[11] has suggested that body length be allowed for in formulas for cardiac output, and Nickerson[3] has included it in a

revised formula for use with his low-frequency instrument.

There is no apparent relationship of the anatomic position of the heart, as measured on anteroposterior teleoroentgenograms, and the magnitude of the longitudinal IJ segment or the magnitude and direction of the frontal plane IJ segment. However, the transverse "IJ" segment appears to be related, at least in part, to the anatomic position of the heart. The greater the asymmetry of the heart, the greater the percentage increase in magnitude of the transverse "IJ" segment after the ingestion of food. We did not study the orientation of the ballistic vector loop in the frontal plane of the body, but the direction of the frontal plane IJ segment reflects this in a general way. Starr and Rawson's[12] analysis of contributions made by various parts of the cardiovascular system to the ballistocardiogram indicated that the major contribution to the ballistic complex came from the flow of blood within the aorta. The movement of blood within the heart during systole played a minor role in the production of the ballistocardiogram. If this is true, the anatomic position of the heart should have little influence on the orientation of the ballistic vector loop, unless the heart is very abnormally placed within the chest.

The importance of the transverse "IJ" segment is not clear. It's basal magnitude does not correlate with body surface area, nor does the magnitude of the frontal plane IJ segment. Simultaneous longitudinal and transverse ballistocardiograms have been recorded in our laboratory since 1950, and during this period of time, more than 1000 ballistocardiograms have been obtained. We have been impressed by the fact that in all the cases in which the longitudinal ballistocardiograms demonstrated normal amplitude, wave pattern and respiratory variation, the amplitude of the longitudinal ballistocardiogram always exceeded that of the transverse ballistocardiogram. Yet, in records obtained from patients with known cardiovascular disease, it is not unusual for the amplitude of the transverse record to exceed that of the longitudinal. The amplitude of the transverse ballistocardiogram is probably of little significance in the normal record, but it appears to assume significance in abnormal records. Perhaps the changes observed in the abnormal transverse record are related to changes in the aorta which are known to occur with age such as decreased elasticity, tortuosity and dilatation. As yet, we have not found a satisfactory method of studying this phase of the problem.

Conclusions

1. In normal males, the correlation of body surface area to the basal longitudinal IJ height is highly significant.

2. Neither the basal magnitudes of the transverse "IJ" nor frontal plane IJ segments correlate with body surface area.

3. The transverse "IJ" segment appears to be related to the anatomic position of the heart.

4. No apparent relationship could be demonstrated between the magnitude of the basal longitudinal IJ segment or the size and direction of the frontal plane IJ segment and the anatomic position of the heart.

5. It is suggested that the probable value of the transverse ballistocardiogram lies in the study of the abnormal record.

Conclusiones in Interlingua

1. In masculos normal le correlation inter area superficial del corpore e altor del basal segmento longitudinal IJ es significativissime.

2. Ni le magnitude basal del transverse segmento IJ ni illo del segmento IJ in le plano frontal se trova in correlation con le area superficial del corpore.

3. Le transverse segmento IJ pare esser relationate con le position anatomic del corde.

4. Nulle evidente relation esseva demonstrabile inter (1) le magnitude del basal segmento longitudinal IJ o le dimension e direction del segmento IJ in le plano frontal e (2) le position anatomic del corde.

5. Nos opina que le valor del ballistocardiogramma transversal es probabilemente su function in le studio del registration anormal.

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The Dynamics of Ventricular Contraction and Relaxation in Patients With Mitral Stenosis as Studied by the Kinetocardiogram and Ballistocardiogram

By E. E. Eddleman, Jr., M.D., Robert H. Yoe, M.D., William T. Tucker, M.D., John L. Knowles, M.S. and Kathryn Willis, M.D.

Kinetocardiograms (precordial movements) and ballistocardiograms were studied in patients with "pure" mitral stenosis. The findings were correlated with catheterization data and clinical findings. Certain characteristics of the kinetocardiograms were presented as well as hypothesis for the movements of the heart and dynamics of ventricular contraction and relaxation in patients with mitral stenosis.

THE purpose of this communication is to present an analysis of the precordial chest-wall movements (kinetocardiograms) and ballistocardiograms in patients with mitral stenosis. The relationship of these events to the movements of the heart and the dynamics of ventricular contraction will be discussed.

Methods

The kinetocardiograms were obtained by the use of a bellows connected by air conduction to a piezoelectric transducer. The pickup arm on the bellows was perpendicular to the chest wall; thus absolute movements of the chest wall could be determined from any point desired. The normal patterns, calibrations, and distribution of forces over the chest have previously been presented.[1, 2, 3] Records were obtained from positions corresponding to electrocardiographic "V" leads and designated as KV_1, KV_2, etc. The kinetocardiograms have been shown to reflect primarily the movements of the heart and are not posteroanterior ballistocardiograms.[4] Volume changes within the chest cavity also probably influence the records during ejection.[3]

Direct displacement ballistocardiograms[5] were recorded with the patient on a sand or putty surface to minimize oscillatory movements.[5] The direct displacement ballistocardiograms as recorded are probably not linear,[6] and, therefore, the amplitudes of the movements are not necessarily proportional to the cardiovascular forces involved. However, time relationships and configuration are reasonably constant.[7] Therefore, the ballistocardiograms are employed principally to indicate the association of precordial movements with headward and footward forces. Carotid pulses, electrocardiograms, kinetocardiograms, and ballistocardiograms were recorded simultaneously with either a Sanborn Poly-Viso or a Cambridge Simpli-Scribe four-channel recorder.

Cardiac catheterization data on six of the patients were available through the courtesy of Dr. R. J. Bing.

Patients

The patients selected for this study were those in whom the diagnosis of mitral stenosis without insufficiency was reasonably certain. Table 1 lists the data on the 13 patients selected. In 10 of the 13 patients the clinical opinion of "only" mitral stenosis was confirmed at operation, in that the surgeon did not feel a "jet" of blood during systole. The other three patients included in this study had typical presystolic crescendo murmurs without the presence of a systolic murmur. All patients who had any evidence of other valvular involvement or in whom the diagnosis of "pure" mitral stenosis was uncertain were excluded. Clinical data on the 13 patients in this study are listed in table 1. Note that the patients had very little difference in their functional impairment. Only two of the patients were not taking digitalis; however, the three patients not operated on were in a somewhat better functional state than those who had the commissurotomy. Postoperative findings will be discussed in a subsequent communication.

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TABLE 1.

Patients	Estimated Size of Valve at Operation (cm.)	Catheterization Data					Electrocardiographic Data			Prominent F-G in Ballistocardiogram*	Fluoroscopic Examination		Clinical Data				
		Right Ventricular Pressure (mm. of Hg)	Pulmonary Artery Pressure (mm. of Hg)	Pulmonary Capillary Pressure (mm. of Hg)	Cardiac Output (L./Min.)	Cardiac Index	Mean QRS Axis	R in V_1 larger than S	R in aV$_R$ larger than Q		Enlargement of Left Atrium	Enlargement of Right Ventricle	Blood Pressure (mm. of Hg)	History of Hemoptysis	Pedaledema	Degree of Exertional Dyspnea	Functional Class†
Group I																	
1	.4	70/0	70 (Systolic)	35 (Systolic)	4.41	2.60	112°	Yes	Yes	(Slight)	1+	0	100/52	Yes	No	Moderate	III
2	.2						122°	Yes	Yes	Yes	3+	1+	130/80	No	No	Moderate	III
3	.2						122°	Yes	No	Yes	2+	3+	105/70	Yes	No	Moderate	III
4	.2	127/40	121/64	40	5.96	4.62	118°	Yes	No	Yes	0	0	100/60	Yes	1+	Mild	III
Group II																	
5	.5		67 (Mean)		5.46	3.03	82°	No	No	Yes	0	0	120/60	Yes	No	Mild	III
6	.5		40/18		7.3	3.53	62°	No	No	No	1+	2+	128/80	No	No	Moderate	III
7	.2	52/6	47/27	29	3.46	2.4	74°	No	No	Yes	1+	0	120/80	Yes	No	Moderate	III
8							75°	No	No	No	1+	0	120/80	No	No	Mild	II
9							90°	No	No	Yes	0	0	120/90	No	1+	Severe	III
Group III																	
10							90°	No	No	Yes	2+	1+	92/80	Yes	No	Moderate	III
11	.4	42/6			6.26	4.1	84°	No	No	Yes	0	1+	95/65	No	2+	Moderate	IV
12							82°	No	No	Yes	0	0	120/70	No	No	Mild	II
13	.6						90°	No	No	Yes	2+	0	118/74	Yes	No	Moderate	II

* The patients indicated with no F-G downstroke did have a small notch present corresponding in time to the marked F-G downstroke noted in the other patients.

† Classification of cardiac function is based on that of the American Heart Association.

RESULTS

Electrocardiograms

Typical electrocardiographic patterns of right ventricular hypertrophy were noted in only 4 of the 13 subjects. The changes were those of right axis deviation; a QR complex in V_1, and a prominent R in aVR. The mean QRS axis varied from 62 to 122 degrees. The majority of the patients had very small R waves in aVR, with the presence of RS complexes in V_1; the R in most instances was less than half the amplitude of the S wave. It is important to note that four patients had an elevation of right ventricular or pulmonary artery pressure in the absence of a typical right ventricular hypertrophy electrocardiographic pattern (table 1). This finding has been noted previously by other investigators.[8]

Kinetocardiograms

There were three types of variations in the precordial movements noted in the 13 patients studied. However, there were certain similarities in the records from all patients with mitral stenosis. For sake of presentation, the features that were common to all will be presented in the following discussion and illustrated in figure 1.

1. An exaggerated initial outward movement of the chest wall (I_1-I_2) that is associated with an exaggerated footward movement (FG) of the body. Approximately 0.04 second after the onset of the QRS complex of the electrocardiogram there occurs a marked outward movement of the lower chest wall (KV_1). In normal subjects it begins earlier (approximately 0.02 second after the onset of the QRS complex) and is of smaller amplitude. Simultaneous with this large outward movement of the chest, there is usually a well-marked footward movement of the body (FG) noted in the ballistocardiogram.

2. An inward movement of the precordium (I_2-E_1) associated with a headward movement of the body (GH upstroke). This inward movement parallels the GH movement of the ballistocardiogram and is noted over the entire anterior precordium. The movement usually begins before the carotid upstroke but extends on into the first part of rapid ejection, terminating approximately at the I point of the ballistocardiogram. One significant feature is that the inward movement rarely goes below the diastolic baseline, except in a few instances which will be discussed subsequently. This is in marked contrast

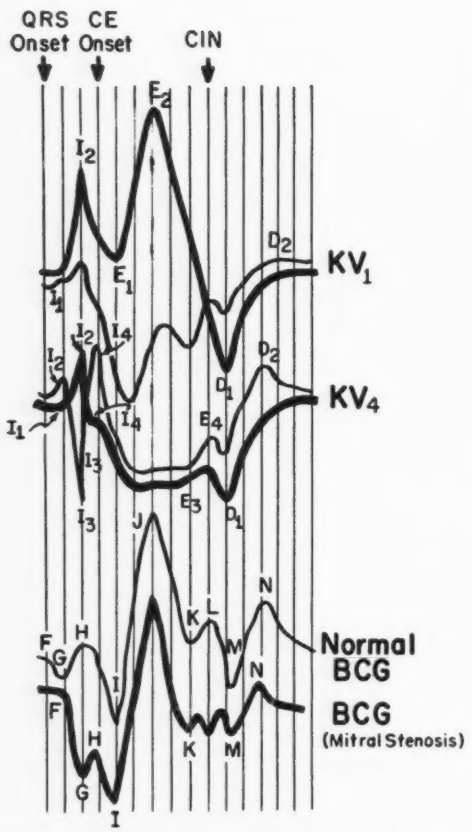

FIG. 1. A drawing of the typical findings in mitral stenosis. The trace from the right parasternal region in the fourth intercostal space (KV_1) is presented as well as the KV_4 tracing from the midclavicular line in the fifth intercostal space. A normal tracing is included for contrast and represented by the fine lines. The vertical lines represent a time interval of 0.04 second. Note that the tracing taken from patient with mitral stenosis has a marked anterior outward movement in the KV_1 area 0.04 second after the onset of the QRS complex. In addition, the precordium in the parasternal area is sustained out above the diastolic baseline during the entire ejection period. This is followed by an inward motion which begins in the terminal portion of systole, extending into the early part of the isometric relaxation phase. The findings are interpreted as indicating a marked anterior or rightward swing of the heart early after the onset of the QRS complex, which probably is the result of right ventricular contraction. This is associated with a footward tug on the body producing the marked F-G downstroke in the ballistocardiogram. The predominance of the contraction of the right ventricle probably results in the precordium being sustained out above the diastolic baseline throughout the ejection period. As right ventricular relaxation occurs the left ventricle pulls the heart posteriorly, producing the inward movement of the precordium which extends into the isometric relaxation phase.

to the patterns noted in normal subjects in which the lower parasternal area retracts during rapid ejection, and the tracing moves well below the diastolic baseline (see fig. 1).

3. The apex thrust. The apex thrust (I_3-I_4) at KV_4 is conspicuously small and on most records is difficult to recognize. Assuming that in patients with mitral stenosis it has approximately the same time relationship to the carotid upstroke as in normal subjects (0.04 to 0.02 second before the carotid upstroke), a small outward movement can be noted over the region of the apex at this time. Since in some instances the anterior swing is directed leftward, there may be an exaggerated outward movement (0.04 second after the QRS complex) which can be confused with the apex thrust. The true apex thrust occurs later (just before the carotid upstroke) and is small or obscured.

4. A prominent outward motion of the chest (E_1-E_2) *paralleling the IJ upstroke in the ballistocardiogram.* The systolic outward movement of the chest wall (E_1-E_2) which parallels the I-J upstroke of the ballistocardiogram is frequently prominent and displaces the anterior chest even further outward during ejection. The chest usually begins moving inward with the JK downstroke; however, *the entire parasternal region of the chest is usually displaced outward and above the diastolic or resting level during the entire period.*

5. An exaggerated inward movement which begins with JK downstroke and extends into isometric relaxation (D_1 point). There is a large inward movement of the chest beginning in most subjects during late systole and extending into isometric diastole. This inward movement is usually pronounced and as a result the chest wall retracts below the diastolic or resting level.

In summary, all patients exhibited an exaggerated but delayed outward motion of the chest 0.04 second after the onset of the QRS complex. There is a well-defined inward motion beginning before the carotid upstroke but often extending into the phase of rapid ejection; however, this is not of sufficient magnitude to retract the chest below the diastolic or resting level in most instances. The inward motion is followed by a second outward motion of the chest wall paralleling the IJ upstroke in the ballistocardiogram and usually displacing the chest further anteriorly during ejection. Thus the entire chest during systole is displaced

anteriorly above its diastolic level, in contrast to a well-marked inward movement in normal subjects.

Variations in the Records. Although all patients had essentially the same features presented in the previous discussion, notable variations did occur. These may be best explained by dividing the patients into three groups. It is emphasized that this division has been done for the sake of presentation and that there is only meager evidence that the groups have any characteristics which are fundamentally different.

Group I: Four patients are classified in this group (table 1). Figure 2 is a drawing and record of the precordial movements (KV_1 and KV_4) and ballistocardiogram from patient 4. The significant features of the records of these four patients are:

1. The initial outward movement of the chest (I_1-I_2) 0.04 second after the onset of the QRS complex was of greatest magnitude over the right lower chest. The lateral chest (KV_5 and KV_6) moved inward simultaneously with the outward motion noted on the right chest.
2. Electrocardiograms typical of right ventricular hypertrophy were noted in these four patients only.
3. Cardiac catheterization in two of these patients revealed elevated pulmonary artery and right ventricular pressures (table 1); however, patient 5 in another group had comparable elevations in pulmonary artery pressure.
4. Two of the four patients had small outward movement (E_1-E_2) paralleling the I-J upstroke of the ballistocardiogram; nevertheless, the parasternal region of the chest was displaced above its diastolic or resting level during systole.
5. The ballistocardiograms were similar in configuration to those previously reported by others in mitral stenosis[9, 11, 19] with a prominent FG downstroke (early marked systolic footward movement). In one subject the FG downstroke was small in amplitude but nevertheless present (patient 1).

Thus the records of these three patients were characterized by a large early anterior movement of the chest wall which was of greatest magnitude over the right lower chest. The chest was sustained out above the diastolic or resting level during systole, in contrast to a well-defined inward movement in normal subjects.

Group II: Figure 3 presents a drawing and record of the kinetocardiograms and ballistocardiograms from patient 8. The four other patients included in this group had similar records (table 1). The variations from those previously presented are:

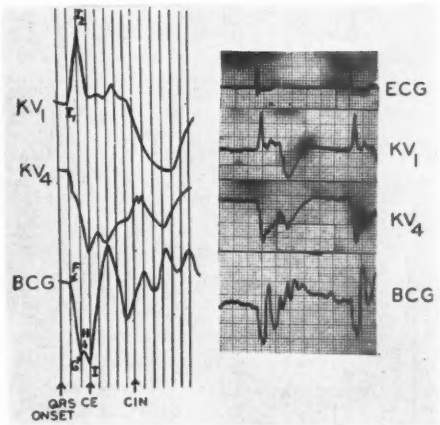

FIG. 2. A trace obtained from patient 4 with a group I type of record. Ce indicates the onset of the carotid upstroke and Cin the carotid incisural notch. Note the marked anterior or outward movement of the precordium 0.04 second after the onset of the QRS complex and the paralleling footward movement (F-G downstroke) in the ballistocardiogram. The parasternal area of the precordium is sustained out above the diastolic or resting level of the chest during the entire ejection period, followed by an inward movement as the right ventricle relaxes, allowing the still contracted left ventricle to pull the heart posteriorly and leftward in the chest. The trace from the KV_4 area demonstrates an inward movement paralleling the outward movement in the KV_1 area. In this instance the anterior swing of the heart is directed more rightward, thus producing the inward motion of the left lateral aspect of the chest. The movements in the kinetocardiogram (KCG) after the P wave and before the QRS complex are prominent in this instance. These movements, although large, are probably not characteristic in patients with mitral stenosis.

1. The early systolic anterior movement (I_1-I_2) occurring 0.04 second after the QRS complex was more pronounced over the left lower anterior chest than on the right. It is important to point out that although this outward movement may be of maximal amplitude in the area of the apex (KV_4), it occurs too soon after the onset of the QRS to be the true apex thrust. In a previous study of comparable age groups the apex thrust was found to occur 0.08–0.10 second[4] after the onset of the QRS complex, or about 0.03–0.04 second before the carotid upstroke. Thus this early outward movement is apparently due

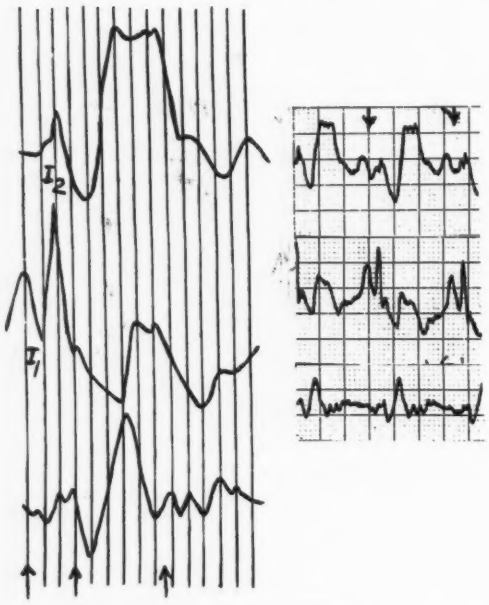

FIG. 3. A drawing of the trace obtained from a patient (Case 8) in group II, in which the anterior or outward movement of the precordium is more pronounced over the left chest than over the right. The arrows on the right-hand figure indicate the onset of the QRS complex. Ce indicates the onset of the carotid upstroke and Cin the carotid incisural notch. The vertical lines represent a time interval of 0.04 second. Electrocardiograms from the patients in group II were not typical of right ventricular hypertrophy and the mean QRS axis was directed more to the left than that noted in the patients in group I. Note the outward movement of the chest 0.04 second after the onset of the QRS complex is most marked in the KV_4 record, indicating the anterior swing of the heart in this instance is directed more to the left than to the right, as noted in group I patients. Although the trace in KV_1 dips slightly below the diastolic baseline during early ejection, KV_2 and KV_3 (not shown) were displaced outward during the entire ejection period, thus lacking the systolic retraction as occurs in normal subject.

to the same mechanisms as the outward movement in the other patients but is directed to the left instead of the right, as noted in group I patients.

2. All five patients had electrocardiograms in which the QRS mean electrical axis was normal (less than 90 degrees). None had typical electrocardiographic record of right ventricular hypertrophy, even in the presence of an elevated mean pulmonary artery and right ventricular pressure (table 1).

3. The inward movement of the kinetocardiogram (I_2-I_3) that parallels the G-H upstroke of the ballistocardiogram moved slightly below the diastolic baseline on the right side of the chest in two patients, but never to the degree noted in normal subjects. Despite the inward movement of the right chest below the resting baseline, the records taken at KV_2 and KV_3 still exhibited a sustained outward motion above the diastolic baseline during systole.

4. The mean outward movement of the chest (E_1-E_2) which parallels the IJ upstroke in the ballistocardiogram was more prominent in these five patients than those in either of the other two groups.

5. The precordial movements following the onset of the P wave in the electrocardiogram were occasionally prominent (fig. 3), with the largest movements noted in the records from the left lower chest (KV_4). However, other patients with a sinus rhythm did not have exaggerated auricular movements, while still others had large outward movements in KV_1 and large inward movements in KV_4. Thus the auricular movements in the kinetocardiograms were variable, and are not characteristically altered in patients with mitral stenosis.

In summary, the patients in group II had initial outward movements of the chest directed leftward, in contrast to its more rightward direction in the patients of group I.

Group III: The last four patients listed in table 1 are included in this group. Figure 4 is a drawing and record obtained from patient 12. These four patients differ from the other patients in the following ways:

1. There was a double outward motion occurring early in systole instead of the single outward motion, as noted in the other patients. The first outward movement began 0.04–0.06 second after the onset of the QRS complex with a duration of 0.04 second, as in the previous patients. This was followed by an abrupt inward motion and then a second outward movement beginning 0.10–0.14 second after the onset of the QRS complex. In two patients the two outward motions were separated only by a small notch in the right parasternal records.

2. The ballistocardiograms in patients of this group had more marked variations than in groups I and II. Two of the patients in group III had notched I-J upstrokes, while one had a very atypical pattern.

3. The mean QRS axis was, in general, intermediate between those noted in the first two groups.

4. Two of these patients had commissurotomies; one patient (case 11) had "pure" mitral stenosis while the other patient (case 13) had an infundibular type of stenosis, with no regurgitation being present in either case. Catheterization data in one was not remarkably different from those in the other groups.

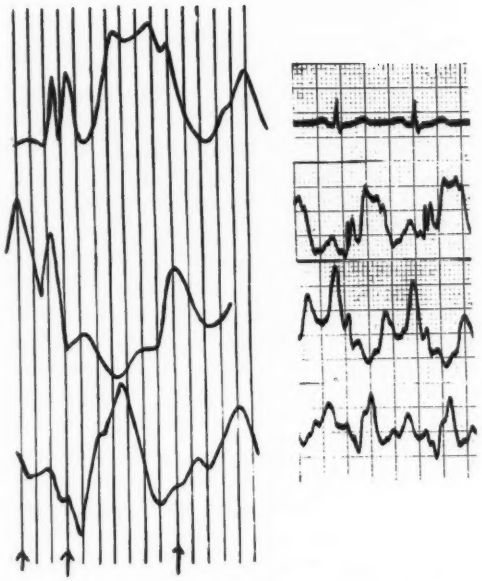

FIG. 4. A drawing and trace obtained from a patient (Case 12) in group III. The time interval between the vertical line is 0.04 second. Ce indicates the onset of the carotid upstroke and Cin the carotid incisural notch. Note that there is a double anterior outward movement of the chest occurring in early systole in contrast to a single anterior movement in the other two groups of patients with mitral stenosis. The records from these patients, nevertheless, still exhibit a marked anterior or outward swing of the precordium, early following the onset of the QRS complex and a sustained outward movement of the precordium during the entire ejection period.

In summary, the patients of group III had two anterior movements of the chest occurring early in systole instead of only one, as noted in the other groups.

Interpretation Based on the Movements of the Heart

The kinetocardiograms have been shown to be related primarily to the movements and shape changes of the heart.[4, 12] Thus, by correlating the various events, a scheme of movements of the heart in mitral stenosis can be postulated. The interpretation is based on a comprehensive study of normal subjects,[12] and is offered as a possible explanation for the various events. Figure 1 is best employed to follow the subsequent discussion.

I. *Exaggerated Anterior Swing of the Heart* (I_1–I_2). The initial outward movement of the chest paralleling the F-G footward movement in the ballistocardiogram is exaggerated in patients with mitral stenosis. This movement is considered to be due to an anterior swing of the heart, as is the comparable movement in normal subjects.[12] It occurs about 0.02 second after the QRS complex in normal subjects but is delayed in patients with mitral stenosis (0.04 second after the onset of the QRS complex). Usually, in normal subjects, it is directed to the right; however, in patients with mitral stenosis it may be directed rightward, anteriorly, or slightly leftward. There is possibly a correlation of the direction of the swing to the mean QRS axis; the patients with right axis deviation had a large outward movement to the right while those with a normal axis tended to swing more to the left. Because the right ventricle is hypertrophied, or at least is the dominating ventricular force in mitral stenosis, it is probable that contraction of the right ventricle lifts the heart anteriorly at this time. This is in keeping with the classic concept that the right ventricle is electrically excited before the left.[13] However, the directional variations of this anterior swing are not easily explained. There are several possible explanations inclusive of the following:

(1) The degree of right ventricular hypertrophy may be a factor, since the patients with typical electrocardiographic patterns of right ventricular hypertrophy tend to swing more to the right. Patients with large right ventricles due to congenital heart disease tend to swing to the right also; however, the records resemble more closely the traces from group III with the double anterior movements than those in group I (anterior swing directed to the right). In addition, there were comparable elevations of intracardiac pressures in the various groups. Thus if the degree of hypertrophy is the determining factor, one must postulate that the elevations of intraventricular and pulmonary artery pressures are not reliable indices of right ventricular hypertrophy. Neither fluoroscopic examination nor the clinical status of the patient has been of help in evaluating the degree of right ventricular hypertrophy.

(2) Another possible explanation is that hypertrophy of the right ventricle may be somewhat asymmetric in location. If the hypertrophy is located more on the right aspects or along the right border of the ventricle, the anterior swing could be

directed rightward as in group I patients. If the hypertrophy is located more on the left aspects, the swing could then be directed leftward as in group II patients.

(3) Alterations in the anatomic arrangement of the muscle fibers could explain the variations in both the kinetocardiograms and the electrocardiograms. Although there is no evidence for this, it can be stated that alignment of the right ventricular fibers in a slightly altered direction would be expected to change the axis of the anterior swing.

(4) The last obvious possible explanation is a variation in the spread of the ventricular excitation wave. Only the variation in the electrocardiograms tends to support this concept.

Preliminary observations seem to suggest that the direction of the initial anterior swing has little effect on the postoperative prognosis. Postoperative findings will be discussed in a subsequent communication.

II. *Apparent Right Ventricular Ejection and Inflow Tract Contraction.* Following the anterior swing of the heart which produces the initial outward movement of the chest, the parasternal area moves inward (I_2–E_1), associated with the G-H upstroke in the ballistocardiogram (fig. 1). The onset of this inward movement in the KV_1 area may be slightly delayed (0.01–0.02 second), as compared with the sharp inward movement in normal subjects. The inward movement in normal subjects is considered to be the result of right ventricular ejection.[12] Thus in patients with mitral stenosis right ventricular ejection may be delayed, as is the anterior swing.

Shortening of the heart in the base-to-apex diameter is not as clearly defined in these patients with mitral stenosis as in normal subjects; however, the inward movement about this time in the apical records may represent shortening. Thus the G-H upstroke which occurs at this time in the ballistocardiogram may represent shortening and inflow tract contraction, with blood displaced at the outflow tracts, as well as headward motion as the result of right ventricular ejection.

In summary, the inward movement possibly represents right ventricular ejection. Shortening of the heart and inflow tract contraction may be an additional factor in the production of this movement.

III. *Apex Thrust* (I_3–I_4). The apex thrust was conspicuously small in all patients and in some instances could not be identified. Often at the time of the expected apex thrust (0.08–0.12 second after onset of the QRS complex) a small notch or outward movement could be detected at KV_4. It has been shown that the apex thrust in normal subjects is probably related to a physiologic shape change with contraction of the thick basilar muscles of the left ventricle, causing a physiologic bulge of the apex.[4] Since the posterior wall of the left ventricle is shortened and atrophied in patients with mitral stenosis,[14] the resulting decreased force of left ventricular contraction could account for the decrease or absence of the apex thrust. An additional factor in the decrease of the apex thrust is the fact that inflow tract contraction and shortening apparently occur late in patients with mitral stenosis, or about the same time as the apex thrust. Thus the inward movement at the onset of apical contraction and the physiologic bulge associated with the contraction of the deep portion of the left ventricle may tend to nullify each other.

IV. *Decreased Systolic Retraction of the Chest* (Ejection portion of I_2–E_1). The predominating force of the right ventricular contraction producing the anterior swing of the heart, and the decrease in cardiac output in patients with mitral stenosis, are both probable factors in decreasing the inward motion of the lower anterior chest during ejection in patients with mitral stenosis. Thus there is only a small inward movement of the chest which rarely dips below the diastolic baseline during early rapid ejection (only two patients had this inward movement go below the diastolic baseline). In the two exceptions, the swing was primarily to the left, while the inward motion occurred over the right chest. In these two patients KV_2 and KV_3 were nevertheless displaced above the diastolic baseline during ejection.

V. *Continuation of Anterior Swing of the Heart* (E_1–E_2). The anterior swing of the heart apparently continues during systole and the chest is displaced even further anteriorly. This usually parallels the IJ upstroke and is

probably due to domination of right ventricular swing over ejection.

VI. *Leftward and Posterior Swing of the Heart* (E_2–D_1). The chest usually begins moving inward about the time of the JK downstroke but in some instances may be sustained outward until approximately 0.04 second before the carotid incisural notch. The inward motion which is most pronounced in the parasternal region is occasionally associated with a smaller outward motion of the left lateral chest. This probably represents the leftward component of the leftward and posterior swing of the heart. The outward motion occasionally noted in KV_4 and KV_5, which begins before the carotid incisural notch and usually terminates with the carotid incisura, probably results from two factors: (1) elongation of the heart (opposite of shortening) and (2) the leftward component of the leftward and posterior swing. This outward motion is never very large and is localized almost entirely to the left lateral chest. The inward motion of the right parasternal region usually continued after the carotid incisura, and is probably the result of right ventricular relaxation, which now allows the heart to be pulled leftward and posteriorly in the chest by the still contracting left ventricle. Thus, because of the marked anterior displacement of the heart during systole, this motion is much more exaggerated than in normals.

VII. *Diastolic Anterior Movement of the Chest* (D_1–D_2). This last outward movement of the chest during early diastole is most noticeable in records taken from the apical region of the chest. It may represent the onset of filling if a sufficient lag is assumed to occur in the jugular "v" wave. As the lag in the "v" wave is probably variable, this hypothesis could not be established definitely. The time of the outward movement was variable, as measured from the carotid incisural notch. However, the mean value fell within the usual values as occur in normal subjects. There was no constant relationship of this movement to the ballistocardiogram.

Summary of the Movements of the Heart in Patients with Mitral Stenosis. 1. Exaggerated anterior swing of the heart due to predominance of right ventricular contraction over left. 2. Delayed right ventricular ejection and inflow tract contraction with shortening of the heart in the apex-to-base diameter. 3. A diminished apex thrust, and a diminished inward movement of ejection. 4. Continued anterior swing of the heart displacing the chest outward during systole as a result of the dominating contraction of the right ventricle. 5. Exaggerated and early leftward and posterior swing of the heart as a result of relaxation of the right ventricle allowing the contracting left ventricle to pull the heart posteriorly and leftward.

Observations Concerning the Genesis of the Ballistocardiogram in Mitral Stenosis

Certain aspects of this study suggest mechanisms which may be responsible for the alterations in the ballistocardiograms of patients with mitral stenosis. The pre-ejection configuration of the ballistocardiogram in mitral stenosis, as presented in the present report (fig. 1), has been pointed out by others.[9, 10, 11] Some patients with mitral stenosis do not have the deep FG but do show an early small footward movement (fig. 3). This FG pattern has been noted in patients with isolated pulmonic stenosis, indicating that it is certainly not specific for mitral stenosis.[15] The association of this movement with the early marked outward movement of the chest suggests it is the result of right ventricular contraction producing a footward tug on the body. The mechanism by which the right ventricle produces this footward tug is not entirely clear. The right ventricle is attached inferiorly by the right auricle to the inferior vena cava and heavy liver structures, and superiorly to the pulmonary artery and great vessels. It is not apparent through which attachment the forces are mediated. The small headward force (GH) following the FG may be partially due to the same mechanism as in normal subjects,[4, 12] apparently the result of shortening of the ventricles and inflow tract contraction with displacement of blood headward into the ventricular outflow tracts. An additional factor in its mechanism may be right ventricular ejection with headward impact on the pulmonary arteries. The HI downstroke which occurs during the initial phase of ejec-

tion is the result of recoil as in normal subjects, but is of small amplitude, possibly due to decreased cardiac output, decreased acceleration of blood, decreased footward tug by the left ventricle, and headward impact of right ventricular ejection.

The diastolic movements of the ballistocardiogram often have three distinct headward waves present (figs. 1 and 2). These movements observed in early diastole have not been previously pointed out.* Although this part of the ballistocardiogram is somewhat unreliable, due to aftervibrations of the body, the movements often are of equal amplitude and lack the appearance of oscillatory movements. Normal subjects may have these movements in the ballistocardiogram using this recording technic,[16] but these movements are never so distinct nor separated as are the movements noted in most of the patients with mitral stenosis. The separation and exaggeration, therefore, may well be due to the release of the excessive footward tug by the relaxation of the hypertrophied right ventricle, thus producing a distinct movement not normally apparent in the normal ballistocardiogram. Again it must be emphasized that these findings, which occur in the ballistocardiogram, are not specific and have been noted in patients with other conditions.

Comments

The kinetocardiograms appear to offer a method by which certain information concerning processes of ventricular contraction and relaxation may be obtained. Thus the development of right ventricular predominance appears to alter significantly the process of contraction and relaxation of the heart with respect to normal subjects, by producing an exaggerated anterior swing during contraction and exaggerated leftward and posterior swing upon its relaxation. Exaggerated anterior swing and the displacement of the chest outward during systole seem to be reliable indices of right ventricular predominance. Similar observations have been noted by Dressler, using other recording technics.[17] It is not clear whether these pulsations represent right ventricular hypertrophy or merely right ventricular dominance over left. Nevertheless, the kinetocardiograms appear to offer a more accurate means of recognizing right ventricular predominance than the electrocardiogram. This is as expected, since the precordial movements represent mechanical effects of the heart instead of electrical events.

Preliminary observations on patients with right ventricular hypertrophy due to other causes suggest that there are similarities between the two, as well as certain differences. Whether the differences are sufficiently specific to warrant a differential diagnosis of right ventricular predominance is still uncertain at the present time. The characteristics pointed out in this study, however, do appear constant in patients with mitral stenosis. These basic movements presented are altered as other types of valvular defects change the load on the heart. Findings in mitral insufficiency will be presented in a subsequent communication.

It is not necessary to discuss the clinical aspects of mitral stenosis, since much has already been written concerning the evaluation and the selection of patients for mitral commissurotomy. The data in table 1 illustrate the limitations of the electrocardiogram and fluoroscopic examination in the study of patients with mitral stenosis.

Conclusions

1. Kinetocardiographic (precordial movements) and ballistocardiographic data obtained from patients with "pure" mitral stenosis are presented.

2. The dynamics of ventricular contraction and relaxation and thus the precordial movements (kinetocardiograms) appear to be significantly altered from that noted in normal subjects.

3. The findings are interpreted as indicating the following events in mitral stenosis: (a) An exaggerated anterior swing of the heart in early systole associated with a footward tug on the body (FG downstroke) as the result of the contraction of the right ventricle; (b) Diminished apex thrust; (c) An exaggerated posterior and leftward swing of the heart in early diastole as the result of right ventricular relaxation, al-

* It is possible that this configuration is only apparent with the damping technic employed in this study.

lowing the still contracted left ventricle to pull the heart posteriorly and leftward.

Conclusiones in Interlingua

1. Es presentate datos cinetocardiographic (movimentos precordial) e ballistocardiographic obtenite ab patientes con "pur" stenosis mitral.

2. Le dynamica de contraction e relaxation ventricular e consequentemente le movimentos precordial (cinetocardiogrammas) pare significativemente alterate in comparation con illo observate in subjectos normal.

3. Le constatationes indica, secundo nostre interpretation, le sequente phenomenos characteristic de stenosis mitral: (a) Un exaggerate propulsion anterior del corde al comenciamento del systole, associate con un traction que se exerce super le corde in le direction del pedes. Isto resulta del contraction del ventriculo dextere. (b) Un diminuite pulsata apical. (c) Un exaggerate propulsion posterior e sinistrorse del corde al comenciamento del diastole. Isto resulta del relaxation del ventriculo dextere e permitte al ventriculo sinistre (que es ancora contrahite) de exercer super le corde un traction posterior e sinistrorse.

Acknowledgment

The authors wish to express their appreciation to Dr. Richard Bing for the catheterization data included in this study.

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Effect of Estrogenic Hormone on Serum Lipids in Patients with Coronary Arteriosclerosis

By ALFRED STEINER, M.D., HENRY PAYSON, M.D. AND FORREST E. KENDALL, PH.D.

The oral administration of large amounts of ethinyl estradial daily to patients with coronary arteriosclerosis and to control subjects consistently produced a favorable effect upon the serum lipid pattern. However, toxic effects of the estrogen prohibited its prolonged use. The clinical status of the patient as evidenced by the incidence of chest pain or the electrocardiogram were not altered during the period of the study.

THE cause of the greater incidence of myocardial infarction secondary to coronary arteriosclerosis in men below the age of 50 as compared with women in the same age group has been the subject of interest and conjecture for many years. The possibility that this difference may be related to endocrine factors which serve to protect the female until the menopause has recently received support by Wuest, Dry and Edwards.[1] These authors observed that the incidence and severity of coronary arteriosclerosis in bilaterally oophorectomized women is greater than in control females, and approaches that found in men.

Many contradictory reports have appeared relating the gonads and their secretions to the serum lipid pattern and to the development of arteriosclerosis both in human beings and in experimental animals.[2] The effect of the administration of estrogens upon the serum lipid pattern of men and women has been studied by a number of investigators. Eilert[3] reported that the oral administration of ethinyl estradiol (0.05 to 0.10 mg. daily) to menopausal women resulted in an average decrease of 25 mg. per 100 cc. in the serum cholesterol level together with an increase averaging 45 mg. per 100 cc. in the serum phospholipid content. Glass and coworkers[4] in a study of 16 men and 15 women in the age group 55 to 65 years found no evidence that estradiol in doses of 0.25 to 0.75 mg. daily for periods of from two to four months influenced the level of either the serum lipids or the low density lipoproteins. Barr,[5] however, reported that the administration of 1 mg. per day of ethinyl estradiol or an equivalent amount of Premarin* to survivors of myocardial infarction was followed by decreases in the serum cholesterol level and increases in serum phospholipid levels. As a result the cholesterol–phospholipid ratio dropped from a mean value of 1.05 to 0.72. This change was shown to be due largely to changes in the concentration and composition of the beta-lipoprotein fraction. Oliver and Boyd[6] found that ethinyl estradiol (0.4 mg. per day) depressed the plasma ester cholesterol in 20 hypercholesterolemic men with coronary artery disease without influencing the serum phospholipid level. Gertler and his associates[7] reported that in 25 patients who received 500 mg. stilbestrol daily following bilateral orchidectomy for carcinoma of the prostate, the serum phospholipid level increased with the serum cholesterol level remaining unchanged.

The majority of these investigations indicate that estrogen therapy produces changes in the serum lipid pattern of patients with coronary heart disease generally considered to be desirable. Further study of this problem is

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* Premarin was obtained from Ayerst, McKenna and Harrison, Ltd.

TABLE 1.—*Effect of Ethinyl Estradiol on Serum Lipids*

Patients		1st Control			Estradiol			Withdrawal			2d Control		
		Range	Mean	S.E.†	Range	Mean	S.E.†	Range	Mean	S.E.†	Range	Mean	S.E.†
1. S. C., 40 yrs.	Neutral fat	80–250	174	20	210–390	313*	16	240–330	255*	7	90–210	159	15
	Cholesterol	190–220	203	3	210–250	225*	3	220–280	271*	4	190–240	205	5
	Phospholipid	200–250	220	5	290–340	306*	6	280–340	310*	10	190–250	228	5
	C/P ratio	0.83–1.03	0.93	.03	0.71–0.77	0.74*	.01	0.77–0.99	0.85	.02	0.78–1.03	0.92	.03
2. J. C., 52 yrs.	Neutral fat	90–270	179	20	130–350	227	18	140–260	191	15	120–210	181	29
	Cholesterol	220–300	258	5	170–280	218*	6	190–320	305*	3	260–310	287*	5
	Phospholipid	220–290	246	5	230–290	268	5	310–360	316*	10	260–320	280*	4
	C/P ratio	1.00–1.10	1.07	.02	0.68–0.97	0.81*	.03	0.77–0.99	0.92*	.04	1.00–1.11	1.04	.01
3. R. G., 54 yrs. (1st study)	Neutral fat	200–340	236	14	220–460	336	29	210–300	245	15			
	Cholesterol	220–230	217	4	170–220	190*	5	210–260	230	3			
	Phospholipid	200–270	230	5	210–260	234	5	220–260	242	10			
	C/P ratio	0.87–1.00	0.94	.02	0.73–0.85	0.82*	.02	0.90–1.02	0.91	.04			
R. G., 54 yrs. (2d study)	Neutral fat	170–280	235	10	220–360	271	10	110–290	206	20	110–270	170	44
	Cholesterol	200–240	225	3	180–230	201*	4	180–290	211	10	180–210	200	6
	Phospholipid	210–260	230	4	220–270	251*	4	190–290	231	10	210–250	230	10
	C/P ratio	0.87–1.04	0.98	.02	0.73–0.95	0.80*	.02	0.72–1.10	0.91	.05	0.80–0.99	0.90	.03
4. S. J., 56 yrs.	Neutral fat	180–300	203	13	160–260	199	11	110–280	210	18	110–250	190	13
	Cholesterol	130–180	163	4	140–160	155	2	170–210	185*	5	190–220	203*	3
	Phospholipid	180–210	190	3	210–270	235*	4	220–270	250*	5	210–260	230*	4
	C/P ratio	0.75–1.04	0.86	.02	0.58–0.72	0.66*	.02	0.63–0.83	0.75	.03	0.76–0.97	0.90	.02
5. G. W., 32 yrs.	Neutral fat	130–400	263	25	230–320	251	18	150–310	220	14			
	Cholesterol	190–240	222	4	160–220	192*	5	200–220	208	3			
	Phospholipid	190–290	235	8	230–310	255	8	210–300	237	10			
	C/P ratio	0.78–1.18	0.96	.03	0.67–0.78	0.74*	.02	0.61–1.05	0.90	.04			
6. A. N., 32 yrs., control	Neutral fat	150–270	197	9	170–350	272*	16	120–450	272	30			
	Cholesterol	190–250	220	5	190–230	217	4	180–250	219	6			
	Phospholipid	200–250	222	3	210–300	263*	8	200–280	240	7			
	C/P ratio	0.79–1.05	0.99	.02	0.76–0.91	0.82*	.02	0.82–1.10	0.93	.03			
7. S. N., 33 yrs., control	Neutral fat	100–200	145	7	120–240	182	10	130–290	209	20	70–180	131	14
	Cholesterol	180–230	201	4	200–240	212	3	210–280	237*	10	200–230	213	3
	Phospholipid	190–250	217	5	260–310	282*	4	250–310	271*	10	220–260	239	6
	C/P ratio	0.87–1.00	0.94	.01	0.71–0.83	0.77*	.01	0.76–0.91	0.87*	.01	0.86–0.98	0.91	.01
8. M. W., 34 yrs., control, 1st study	Neutral fat	60–200	127	16	100–340	243	37	70–270	170	20	80–190	139	10
	Cholesterol	160–190	176	3	150–160	157*	2	170–240	212*	6	180–240	200	4
	Phospholipid	190–220	203	4	200–230	215	4	220–270	237*	5	190–240	211	4
	C/P ratio	0.82–0.92	0.87	.02	0.70–0.83	0.74*	.02	0.70–1.01	0.89	.03	0.90–1.06	0.97*	.02
M. W., 34 yrs., control, 2d study	Neutral fat	90–210	156	20	130–310	218	14	110–220	152	12	90–310	155	21
	Cholesterol	170–200	190	3	180–200	190	2	200–240	215*	3	190–230	202	4
	Phospholipid	190–210	200	3	200–270	246*	5	230–270	247*	6	200–240	211	3
	C/P ratio	0.90–1.03	0.94	.02	0.72–0.90	0.78*	.02	0.76–0.97	0.88	.02	0.88–1.09	0.97	.02

* Statistically different from 1st control values; $p < .01$.

† Standard Error of the Mean = $\frac{Standard\ Deviation}{\sqrt{N}}$.

indicated and the following observations on the effect of estrogens upon the serum lipids and the clinical state of males with significant coronary arteriosclerosis were made.

METHOD

Five male patients, aged 32 to 56, with coronary arteriosclerosis (well documented myocardial infarction) and three male patients, aged 32 to 34, with inactive multiple sclerosis, spastic paraplegia, and paralysis from old poliomyelitis, respectively, were studied. The patients were hospitalized and maintained upon a constant diet of 2000 calories containing 85 Gm. each of protein and fat. An initial control period of four weeks was followed by from 18 to 62 days of estrogen therapy* by mouth. The daily dosage varied from 0.25 to 1 mg. of ethinyl estradiol per day and was governed by the patient's ability and willingness to tolerate the medication. The four weeks period subsequent to the medication was arbitrarily designated the withdrawal period and was followed in most cases by a second control period. Two of the patients were studied through two courses of medication.

Blood was drawn in the fasting state twice weekly during the course of the experiment. Serum cholesterol was determined by the method of Schoenheimer and Sperry,[8] serum lipid phosphorus by the method of Fiske and Subbarow[9] and total serum lipid by a gravimetric procedure. Serum phospholipids were calculated by multiplying the serum phosphorus by a factor of 25. The neutral fat content of the serum was estimated by sub-

* Ethinyl estradiol, Estinyl (Schering).

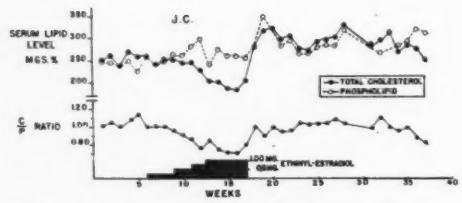

FIG. 1. Effect of estrogenic hormone on serum lipid pattern of patient J. C.

tracting the sum of the phospholipids, the cholesterol and the fatty acids combined with cholesterol, from the total lipids. The estrogen therapy was considered to have produced a significant alteration of serum lipid levels only when the mean level during the treatment or withdrawal periods differed from the mean level of the control period by at least three times the standard error of the difference between the means ($p < .01$.).

RESULTS

The results of this study are summarized in table 1 and figure 1 which give the ranges, the mean values, and the standard error of the mean values of the serum levels of neutral fat, total cholesterol and phospholipid and of the cholesterol–phospholipid ratio during the control, experimental, and withdrawal periods. The administration of ethinyl estradiol produced a fall in the serum cholesterol level in 5 of the 10 trials and an increase in concentration of phospholipid in six trials. However the changes were such as to produce a significant lowering of the cholesterol–phospholipid ratio in every case. One month later the levels had fallen toward the control range. The effect of ethinyl estradiol on the serum lipid levels of the control patients did not differ from that seen in the patients with proven coronary arteriosclerosis.

All of the patients in this study developed toxic effects from the ethinyl estradiol in the dosage given. These effects consisted of fatigue, loss of appetite, nausea, vomiting, enlargement and sensitivity of the breasts and loss of libido. In several instances the estrogen had to be reduced in dosage or discontinued because of these reactions.

There was no evidence of improvement in the clinical status of the five patients with coronary arteriosclerosis during this study. No change either in the electrocardiographic findings or in the incidence of chest pain was observed during and following the estrogen treatment.

DISCUSSION

The results of this study confirm the findings of other investigators that oral administration of ethinyl estradiol to male subjects is followed by changes in the serum lipid pattern. The serum levels of cholesterol, phospholipid, and neutral fat of all the patients used in this study were well within the range of values found for healthy adults. The only abnormality in the lipid pattern observed during the initial control period lay in the somewhat high values found for the cholesterol–phospholipid ratio. During the period of ethinyl estradiol administration the serum cholesterol level fell significantly in five cases and the phospholipid level rose significantly in six cases. These changes were distributed in such a way as to produce a lowering of the cholesterol–phospholipid ratio in all the cases.

An increase in the serum level of neutral fat has previously been reported as a result of estrogen administration in patients with biliary cirrhosis by Ahrens, Payne and Kunkel.[13] A similar increase was observed in six instances in this study. However, the precision of determination of the serum level of neutral fat is low since the value is derived by subtracting the phospholipid, free cholesterol and cholesterol ester from the total lipids and thus includes the experimental error of four difference measurements.

During the withdrawal period the levels of cholesterol and phospholipid tended to rise to values higher than those observed during the control period. This is suggestive of the rebound seen during convalescence from a febrile illness[10] or after withdrawal of thyroid therapy.[11] A similar rebound is not seen when lowered serum cholesterol levels occur as a result of diets low in fat and cholesterol. After the return of the patient to a normal diet the cholesterol level rises to but not above the control value.[12]

It should be pointed out, however, that

certain differences exist between the results obtained in this study and those recorded in the two most recent reports. Gertler and his coworkers[7] found that the serum phospholipid level increased while the serum cholesterol level remained unchanged in 25 patients given 500 mg. of stilbestrol daily and who had previously been subjected to bilateral orchidectomy for carcinoma of the prostate. However, Oliver and Boyd[6] reported that a fall in serum cholesterol occurred without a change in the serum phospholipid after the oral administration of 0.4 mg. estradiol daily to patients with coronary arteriosclerosis. The reports by Eilert[14] and Barr[5] recorded alterations in both the serum cholesterol and serum phospholipid as are reported in the present study.

Nothing can be stated with certainty about how ethinyl estradiol acts to produce these changes in the serum lipid pattern. It may have a direct effect upon the metabolism of the lipids. It may operate by disturbing the whole endocrine balance which governs these metabolic processes.

The limited data available at this time, do not indicate that estrogen therapy has a beneficial effect upon the course of coronary arteriosclerosis. It is true that during the period of estrogen administration the serum cholesterol and phospholipid levels of patients tend to approach the levels found in young healthy adults. Further work is required to show that this shift improves the prognosis of patients with coronary arteriosclerosis.

It is possible that study of the mechanisms involved in this action of estrogens may lead to the discovery of agents which can accomplish the same results without producing the distressing side effects that preclude the widespread use of this drug.

Summary

The oral administration of 0.25 to 1 mg. of ethinyl estradiol daily to patients with coronary arteriosclerosis and to control subjects consistently produced a significant fall in the cholesterol–phospholipid ratio. This change was due to the lowering of the serum cholesterol level without much change in the phospholipid level in 5 of the 10 experimental periods. It was due to increased phospholipid levels without significant changes in the cholesterol levels in the other five instances. Serum neutral fat levels increased in 8 of the 10 periods studied. Toxic effects of the estrogen prohibited its prolonged use, except as a tool for investigative study. There was no change in the incidence of chest pain or in the electrocardiogram in the patients with coronary arteriosclerosis during the period of observation.

Summario in Interlingua

Le administration oral de 0,25 a 1,0 mg ethinyl-estradiol per die resultava, tanto in patientes con arteriosclerosis coronari como etiam in subjectos de controlo, in un reduction significative del proportion de cholesterol a phospholipido. Iste cambiamento reflecteva, in 5 del 10 periodos experimental, un reduction del cholesterol seral sin grande variationes in le nivellos de phospholipido. In le caso del altere 5 periodos experimental, illo reflecteva un augmento de phospholipido sin significative variationes in le nivellos de cholesterol. Le nivellos de grassia neutre del sero accresceva in 8 del 10 periodos studiate. Le effectos toxic del estrogeno non permitteva su uso prolongate excepte como instrumento investigative. Durante le periodo de nostre observationes nulle cambiamento esseva notate in le frequentia de dolores thoracic o in le electrocardiogrammas del patientes con arteriosclorosis coronari.

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Dye Dilution Curves and Cardiac Output in Newborn Infants

By KLARA J. PREC, M.D. AND DONALD E. CASSELS, M.D.

The pattern of dye dilution curves and the cardiac output was studied in 29 healthy newborn infants during the first 26 hours of life by the method of Wood and his associates. Thirty-six per cent of all infants studied had curves of normal contour which occurred mostly in infants older than 15 hours. Infants younger than 15 hours tended to have curves of abnormal shape. These were either diphasic or had the appearance of curves associated with left-to-right shunts and were probably caused by a patent ductus arteriosus. The mean cardiac output was 540 cc. per minute.

THE study of the physiology of the cardiovascular system in newborn infants has been limited because of the technical difficulties encountered in trying to apply methods used in adults. The dye dilution method of Hamilton[1, 2, 3, 4] as modified by Wood and his associates[5, 6] seemed to be a relatively simple approach to the study of these problems. We have used this method to study the pattern of dye dilution curves and to determine the cardiac output of infants during the first two days of life. We believe that the results obtained from the study of the contour of dye dilution curves and the relationship of the various components of these curves also give information that may be of help in detecting the persistence of one or more fetal channels during the early neonatal period.

MATERIAL

Twenty nine healthy newborn infants, age 2 to 26 hours, were included in the study. Each infant was studied asleep with its head and chest placed under an "oxyhood" into which oxygen was delivered at a flow of 7 liters per minute. Infants who were restless or crying were not included in the study.

METHOD

A Brush recorder was used in conjunction with the Wood earpiece oximeter for the continuous recording of the dilution pattern of Evans-blue dye (T-1824) following almost instantaneous injection of this dye into the umbilical vein. The single scale method only was used. The amount injected was calculated on the basis of 0.4 to 0.5 mg. per kilogram of body weight and was usually between 0.2 to 0.5 cc. of a 0.5 per cent solution of T-1824. The exact amount of dye was injected through a polyethylene catheter by means of a syringe which had been calibrated to deliver without flushing. The umbilical vein was chosen for injection because peripheral injection through a needle is difficult in newborn infants and cannot be done under the ideal basal conditions of sleep. Immediately before the actual injection of dye blood was aspirated through the catheter to make certain that the catheter tip was in a position where blood was circulating freely. It was soon realized, however, that the anatomical position of the catheter tip and therefore of the injection site varied in different infants. In some instances the catheter could be advanced without meeting resistance, but in others obstruction was quickly met and it was necessary to maneuver the tip to get a free flow of blood. This variability in the position of the catheter is well shown on films of the abdomen of two newborn infants with radio-opaque catheters introduced through the umbilical vein (figs. 1 and 2). The significance of this will be discussed later.

Cardiac output was determined by a modification of the method described by Nicholson and Wood,[6] using ear oximeter dye curves and calculating the output from the Hamilton equation,

$$\textit{Cardiac output} = 60I/CT$$

where I represents the amount of dye injected in milligrams; T, the duration of the primary curve in seconds; and C, the mean concentration of dye during its initial passage through the ear in milligrams per liter of whole blood). The ear oximeter curves were calibrated by these authors by adding known quantities of T-1824 to arterial blood samples or to venous samples arterialized in a tonometer which then were drawn through a cuvette oximeter to

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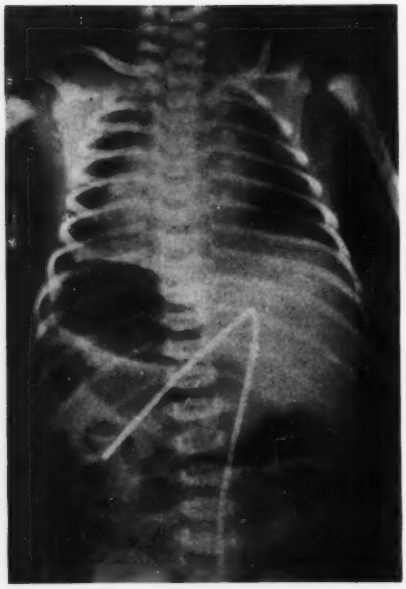

FIG. 1. Radio-opaque catheter introduced through the umbilical vein. The tip of the catheter is located in one of the mesenteric veins.

FIG. 2. Radio-opaque catheter introduced through the umbilical vein. The tip of the catheter is located within the liver substance.

record the corresponding deflection. Measurements of dye curves were made with a planimeter. To avoid the drawing of relatively large amounts of blood from small infants, the calibration of ear oximeter curves was modified.

Two 5-cc. samples of blood were withdrawn from a peripheral vein (from the umbilical vein in newborn infants) one before and one five minutes after intravenous injection of a calculated amount of T-1824. It was assumed that mixing of the injected dye with the circulating blood volume was completed in five minutes. The time of each withdrawal was marked on the moving chart paper of the recorder. Blood samples were centrifuged for 30 minutes at 3000 revolutions per minute. The plasma was withdrawn and the dye concentration of the five-minute sample determined in a Colemann spectrophotometer by comparison with a sample of dye-free plasma to which a known amount of dye had been added. Hematocrit values were obtained simultaneously by the Wintrobe method. These were used to calculate the dye concentration in whole blood. The relation between the dye concentration of the blood sample so determined and the deflection of the ear oximeter at the moment the blood sample was drawn was used to determine dye concentrations at other points on the dilution curve. This method removes the need for using arterial or arterialized blood for calibration. In a small group of children both venous and arterial blood samples were withdrawn simultaneously and used for quantitation of dye curves in this manner. In all instances the results were identical, and, therefore, it was considered satisfactory to use venous samples only in the study of newborn infants. Unfortunately it was not possible to check the accuracy of this modified dye dilution method against results by other methods because accepted methods for cardiac output determination are not suitable for use in healthy infants and children.

One difficulty was encountered, which may influence the accuracy of the results. This was a change in the IR reading of the galvanometer which occurred after injection of T-1824. Readjustment of the IR setting to its preinjection level resulted in a decrease in the distance between the recorded oximeter deflection and the original baseline in every instance. Two explanations for the change in IR reading may be advanced. Although the mechanical baseline appeared to be stable before the dye was injected, it is possible that it may have drifted downward gradually during the five-minute interval before the calibration sample was drawn. Since this would be a gradual change, it would not affect appreciably the depth of the curve recorded during the primary circulation and could be corrected for in the calibration sample by resetting the IR reading before drawing the blood. The other explanation assumes a direct effect of the dye on the hemoconcentration of the blood. Some foundation for this assumption lies in the fact that hematocrit values of blood withdrawn five minutes after injection of the dye were consistently lower (1 to 1.2 percentage

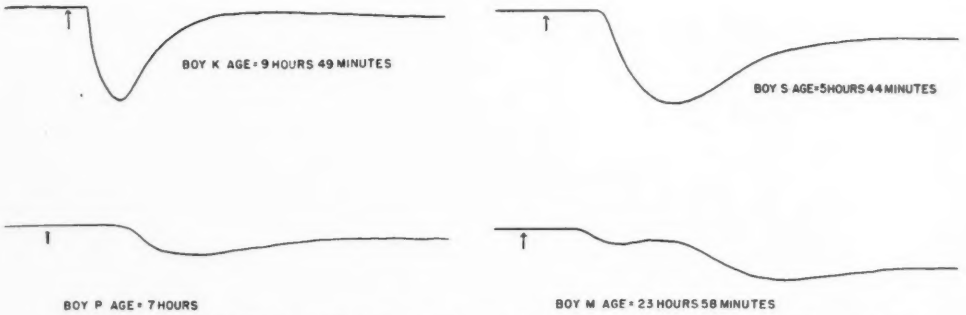

FIG. 3. Types of T-1824 dye dilution curves found in healthy newborn infants 2–26 hours of age. The upper two curves are normal in contour. The curve on the left corresponds to a higher cardiac output, the one on the right to a lower cardiac output. The two curves below are abnormal in shape. The curve on the left has a prolonged disappearance time such as is found in patients with left-to-right shunts. The curve on the right is a diphasic curve consisting of a small shallow primary curve followed by a larger and deeper recirculation curve.

points) than of the preinjection sample from the same patient. Such a decrease in hematocrit values might be expected to increase the infrared light transmission of the oximeter. Other authors[7] also noted increases in infrared light transmission following injection of T-1824, but in their cases this was associated with increased hemotocrit values measured at the peak of the dye curve. They were unable to explain the increased IR light transmission to their satisfaction. Whatever the correct explanation may be, experience in our laboratory showed that impossible values of cardiac output were obtained if the IR setting was not readjusted. Consequently it was decided to readjust this setting before drawing the calibration samples.

Cardiac index was determined by dividing cardiac output by surface area. The Du Bois formula,

$$A = H^{0.725} \times W^{0.425} \times 71.84$$

was used. A represents the surface area in square centimeters, H, the height in centimeters and W, the weight in kilograms. As a matter of interest we have compared the results calculated by the method described above with those calculated by the empirical triangle method of Warner and Wood.[8] The mean values for cardiac output as calculated by the two methods were not significantly different. However the standard deviation of the percentage differences between results by the two methods was 17.7 per cent in a group of seven healthy children and 35 per cent in a group of 10 healthy newborn infants.

RESULTS

The most remarkable finding was the lack of uniformity of contour of the dye dilution curves obtained in the group of 29 healthy infants during the first 26 hours of life. Since all infants were studied under the same basal conditions, this variation in the curves must have been related to changing circulatory patterns during the first few hours of life. Upon plotting these curves on semilogarithmic paper it becomes obvious that there are three general types of dye dilution curves in the newborn, (1) normal, (2) left-to-right shunt, and (3) diphasic (figs. 3 and 4).

1. Normal Curves. Ten infants had normal curves. Four of these infants were under 15 hours of age. Normal curves were characterized by the same smooth outline as curves found in healthy individuals of any age, usually with a somewhat more rapid downward than upward deflection. The length of the appearance time, build up time and disappearance time varied little within this group, with average values of 3.22, 4.9 and 7.99 seconds respectively and seemed within the expected range for the age. The mean ratio between the disappearance time and build up time (DT/BT) was 1.66. In a few instances the appearance time seemed extremely short (1.55, 1.6, 2.3 seconds). Generally speaking curves in this group appeared unexpectedly large. The average peak height was 33.8 mm., corresponding to a mean peak concentration of 14.73 mg. per liter of blood. Because the amount of dye injected per kilogram of body weight varied somewhat in different infants, peak height values were corrected on the basis of an assumed injected amount of 0.4 mg. of T-1824 per kilogram of body weight. The average corrected peak

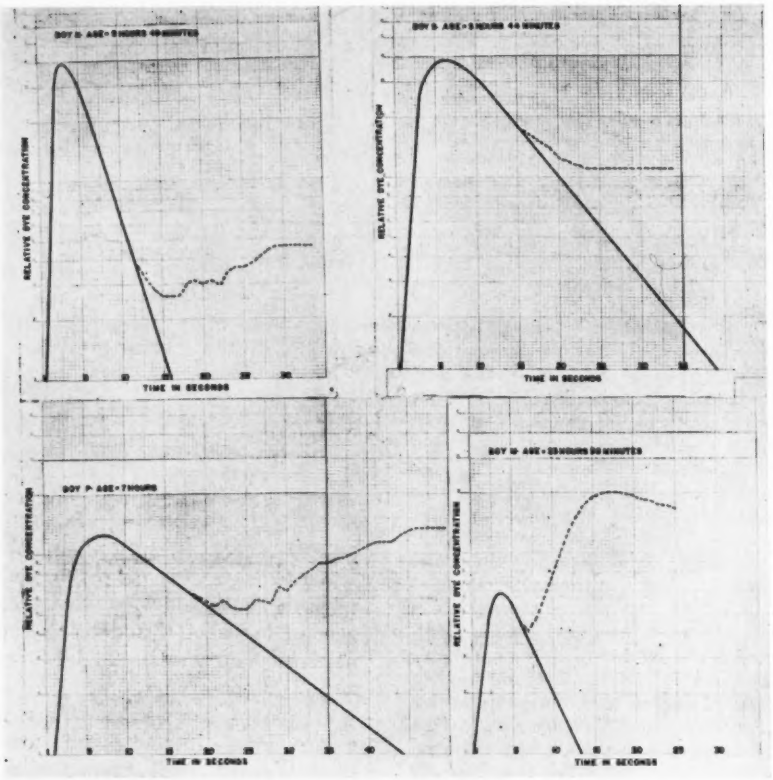

FIG. 4. The same curves as shown in figure 3 plotted on semilogarithmic paper. The differences in contour between the various dye dilution curves are clearly seen. Primary curves are represented by solid lines, recirculation curves by broken lines.

height was 33.0 mm. and the corrected peak concentration 14.9 mg. per liter. Since the size of a dilution curve depends largely on the amount of dye injected it is probable that in some infants the amount injected was too large. However, smaller quantities of T-1824 could not be used since in infants with left-to-right shunts the curves were rather small and shallow with the amounts used and it is not possible to anticipate the type of curve which will be obtained. Another factor which is known to influence the size of the curve is the site of injection, central injections giving rise to curves of greater height than peripheral injections.[9] Since the injection site was not uniform because of the varying position of the catheter tip after it was introduced into the umbilical vein, the question arose whether dye could have been injected through a patent ductus venosus. This would represent a more direct pathway to the heart than if dye were injected into one of the branches of the umbilical vein or the portal vein with the ductus venosus closed. It seems unlikely that the ductus venosus was patent in all infants with normal curves particularly since normal curves occurred with greater frequency in the older infants where one might expect the ductus venosus closed more frequently. The contour of the normal curves was broader and shallower in infants with a lower cardiac output and narrower, more peaked in those with higher output. This is similar to findings in older individuals.

2. Left-to-Right Shunt Curves. Twelve infants studied had dilution curves resembling curves

TABLE 1.—*Comparison of Time Components and Peak Heights of Evans-blue Dye (T-1824) Dilution Curves From Healthy Newborn Infants with a Central Left-to-Right Shunt Due to Atrial Septal Defect, Ventricular Septal Defect and Patent Ductus Arteriosus. Diagnosis of All Cardiac Lesions was Confirmed by Cardiac Catheterization*

		1–19 Years			Newborn (2:45–26:47 hours)		
		Normal	Interventricular and atrial septal defects	Patent ductus arteriosus	Normal	Left-to-right shunt curves	Diphasic curves
Number of Cases		18	13	6	10	12	7
Appearance time (seconds)	mean	7.66	6.5	6.7	3.22	5	4.1
	range	4–12.4	4.2–8.4	4.1–8.4	1.6–4.4	2.4–6.2	2.6–5.0
	S.D.	±2.021	±1.313	±7.081	±1.110	±1.103	±0.856
Build-Up time (seconds)	mean	5.70	6.48	5.0	4.89	5.3	4.18
	range	2.8–7.6	4.9–9.5	3.6–6.6	2.7–6.6	3.3–7.1	3.0–5.2
	S.D.	±1.421	±1.405	±5.332	±1.298	±1.237	±0.692
Disappearance time (seconds)	mean	7.32	29.0	10.7	7.99	17.4	9.38
	range	2.1–11.9	10.2–69.5	8.2–15.2	4.8–13.4	8.6–47.1	5.6–21.9
	S.D.	±2.785	±18.223	±2.537	±2.568	±10.800	±5.685
Ratio, $\frac{\text{Disappearance T.}}{\text{Build-up Time}}$	mean	1.28	4.53	2.10	1.66	3.2	2.26
	range	0.68–1.8	2–12.2	1.44–2.9	0.79–2.14	2.34–8.40	1.45–5.34
	S.D.	±0.388	±2.555	±0.640	±0.437	±1.696	±1.372
Peak height of dye curve corrected to 0.4 mg./Kg. (mm)	mean	33.15	18.90	26.85	33.00	9.05	9.62
	range	16.2–62.8	10.35–31.32	11.97–48	16.1–52.1	3.6–26	5.2–18.4
	S.D.	±11.61	±8.001	±15.942	±9.672	±6.110	±5.012

associated with left-to-right shunts. All of these infants were under 15 hours of age. Curves in this group were rather shallow and more prolonged than in the group with normal curves and the time components were generally longer while concentration components were smaller. The main characteristic was a markedly prolonged disappearance time. The mean values for appearance time, build up time and disappearance time were 5, 5.3 and 17.4 seconds, respectively. The mean disappearance time–build up time ratio was 3.2, peak heights averaged 11.75 mm. and corrected peak heights 9.05 mm. Peak concentrations which were calculated only in five infants of this group had a mean value of 6.65 mg. per liter, with a corrected mean value of 6.4 mg. per liter.

Broadbent, Clagett, Burchell and Wood[10] pointed out that an inverse correlation exists between the peak concentration and the magnitude of the A-V shunt, while a direct correlation is found between the disappearance time–build up time ratio and the size of the shunt. In order to estimate the size of the shunt the average peak concentration and disappearance time–build up time ratio were compared with values found in a group of 13 children (1 to 13 years) with interventricular and interatrial septal defects and with those from a group of six children (1½ to 15 years) with patent ductus arteriosus (table 1). It appears that the amount of blood shunted in newborns was in most instances moderately large.

3. Diphasic Curves. In seven infants, varying in age between 6 and 24 hours, peculiar diphasic curves were obtained. These were characterized by a small primary curve and a rather deep recirculation curve. The primary curve had either a normal contour or the contour characteristic of a left-to-right shunt. The recirculation curve had a greatly prolonged downstroke and the upstroke in most cases was barely visible and fused indiscernibly with the final recorded line which follows injection of dye. The average values for the components of the primary curve were as follows: appearance time 4.1 seconds, build-up time 4.18, disappearance time 9.38 seconds, disappearance time–build up time ratio 2.26, peak height 12.54 and corrected peak height 9.62 mm. The recirculation time, which is the distance between the peaks of the primary and recirculation curves and corresponds to the mean ear to ear circulation time, differed in

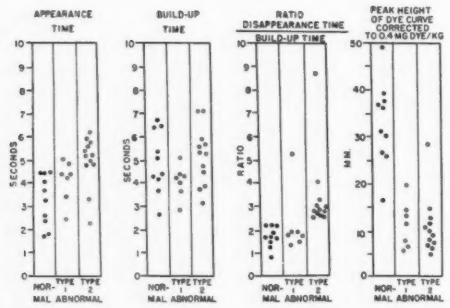

FIG. 5. Comparison of time components and peak heights of normal and abnormal dye dilution curves in the newborn. The abnormal curves are either diphasic (type 1) or of the left-to-right shunt type (type 2).

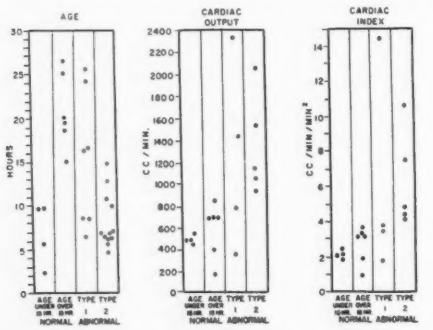

FIG. 6. Age distribution of normal and abnormal dye dilution curves in the newborn. Abnormal curves are subdivided into types 1 and 2, diphasic and left-to-right shunt types, respectively. Values of cardiac output and cardiac index calculated from normal and abnormal dye dilution curves. The majority of those calculated from abnormal curves is outside the physiological range.

every infant (13.9, 24.9, 18.8, 30.2, 24.4 seconds; in two infants it was impossible to measure). Plotting these curves on semi-logarithmic paper showed particularly well the difference in peak heights between the primary and recirculation curves. The impression gained from these curves was that only part of the injected dye reached the ear on its first circulation, which would explain the rather small primary curve, while the remainder of the dye showed up later. The reason for this delay in appearance of dye is difficult to explain. It is conceivable that there was some peripheral pooling of dye in the liver, although prior to injection of dye we always made sure by aspiration of blood that the catheter tip was in a position where blood was flowing freely. It may have been due to an artefact caused by some mechanical defect in the recording which cannot be accounted for. Finally, it is quite possible that these diphasic curves represent a right-to-left shunt through a patent ductus arteriosus. Since pressure differences between the pulmonary artery and the aorta are assumed to be small during the first few days of life, the pulmonary artery pressure might at times exceed the aortic pressure and give rise to a right-to-left shunt through a still patent ductus arteriosus. In that case part of the injected dye would not reach the ear on its first circulation but would flow through the ductus distally and would appear at the ear only after more thorough mixing had occurred.

4. Cardiac Output. The cardiac output and cardiac index were calculated in 10 infants with normal dye dilution curves. The average value for cardiac output was 547.7 cu. mm. per minute with a range from 186 cc. to 854 cc. Cardiac index values varied between 0.9 and 3.7 with an average of 2.5. Infants younger than 15 hours tended to have a lower output than older infants (figs. 5 and 6). Various authors in the past have estimated the cardiac output of newborn infants on the basis of a number of theoretical considerations and arrived at values between 440 cc. and 520 cc. per minute.[11, 12, 13, 14] These figures are similar to those of the present study. For comparison the cardiac output in five newborn infants with abnormal curves suggesting a left-to-right shunt and in four infants with diphasic curves were calculated. The average cardiac output and cardiac index in the first group was 1341 cc. per minute (range 934 to 2050) and 6.36 (range 4.1 to 10.5), respectively. In the second group the mean cardiac output was 1244 cc. per minute (range 343 to 2320) and cardiac index 5.93 (range 1.8 to 14.4). As one might expect, values in both groups were excessively high and outside the physiological range.

DISCUSSION

It seems necessary to find a plausible explanation for the occurrence of abnormal types of curves in normal newborn infants.

Most likely they are due to some fetal channel not yet closed, particularly since the incidence of these curves diminishes in infants older than 15 hours. It is generally thought that with the onset of breathing pulmonary resistance decreases, thereby permitting a larger amount of blood to reach the lungs. The increased amount of blood which returns from the lungs raises the left atrial pressure and thereby closes the valve guarding the foramen ovale. The foramen ovale then remains physiologically closed, anatomical closure following later. The mechanism of closure of both the ductus arteriosus and ductus venosus is incompletely understood. The exact time of physiological closure of any of the fetal pathways has not been proven in the human newborn, although a great deal of information has been gained from the work of Barclay, Barcroft and others who studied the closure of these channels in animals, particularly in lambs (15, 16). Their findings are, however, not necessarily applicable to the human infant.

The effect of the persistence of any of the three fetal channels, foramen ovale, ductus arteriosus, or ductus venosus, upon the size or shape of the dye dilution curve can best be discussed by considering separately each type of curve found in this group of newborn infants. Curves with normal contour are of rather large size and in three of these curves the appearance times seem excessively short: 1.5, 1.6, and 2.3 seconds. The reason for this is not easily explained. It is conceivable that in these three infants the circulation rate was very fast, due to a rapid heart rate, thus causing the injected dye to appear at the ear oximeter site more rapidly. Evidence for this is not available since heart rates were not recorded simultaneously with the dye injections. Another possible explanation for the very short appearance time is that T-1824 was injected through a patent ductus venosus, reaching the inferior vena cava directly instead of having to pass through the capillary bed of the liver before reaching the right atrium. An attempt to determine the patency of the ductus venosus was made by introducing a radio-opaque catheter through the umbilical vein and taking x-ray pictures in two infants. In one infant the catheter passed into a mesenteric vein and in the other it was located in the liver, but the ductus venosus was not entered. This study, therefore, offers no positive evidence that the ductus venosus does not close immediately after birth, although it does not exclude that possibility. The question arose whether the very short appearance times could have been caused by a right-to-left shunt through the foramen ovale. We think this unlikely since the curves in question had a smooth outline without the usual double hump on the downstroke found in the presence of right-to-left shunts. A smooth curve could result under these circumstances only if the catheter tip were located right at the opening of the foramen ovale and all dye were injected into the left atrium. It is extremely doubtful that the catheter tip reached this position. The fact that a double hump curve has not been observed in the present study argues against the presence of right-to-left shunts in the newborn infant under the conditions of the test, i.e. with the infant asleep. Lind and Wegelius,[17] who studied the circulation in newborn infants by angiocardiography, were able to show the presence of small right-to-left shunts through the foramen ovale during the first six days of life. Prec and Cassels[18] also found good evidence for such shunts while studying changes in arterial oxygen saturation in newborn infants during crying. The most probable reason why such a shunt was not demonstrated in the present study was that infants were studied while asleep. Under these conditions it is less likely that blood is shunted from the right to the left atrium through the foramen ovale since the right atrial pressures tend to be lower than the left atrial pressures. During crying this normal pressure relationship is frequently reversed and can lead to a right-to-left shunt during the early newborn period when the foramen ovale is not anatomically closed. It seems possible that infants studied by Lind and Wegelius were either crying during the angiocardiography or else that the normal atrial pressure gradient was reversed by injection of a relatively large amount of contrast material into the right atrium.

The most interesting finding in our present

study was the occurrence of left-to-right shunt curves in a number of newborn infants under 15 hours of age. The injection site seems to be unimportant in the production of these curves. Since a left-to-right shunt curve was also

FIG. 7. T-1824 dilution curve of infant A., 4 hours 8 minutes old. The dye was injected into the right antecubital vein.

obtained after injection of dye into the antecubital vein of a newborn infant 4 hours 8 minutes old (fig. 7). A patent ductus venosus could hardly give rise to this particular type of curve nor is it likely that a left-to-right shunt could occur through a patent foramen ovale. The latter opening is guarded by a valve which closes at birth due to increased filling pressure in the left atrium. Because of the anatomical position of this valve it seems improbable that an appreciable amount of blood could be shunted from the left into the right atrium through the foramen ovale as long as this valve is intact. By exclusion our evidence favours the presence of a patent ductus arteriosus through which a left-to-right shunt could occur as soon as the aortic pressure exceeds the pulmonary artery pressure. The average systemic blood pressure at birth measured in the umbilical arteries is about 80/46 mm. Hg, and the systolic pressure increases within the first 24 hours by about 10 mm. and by another 10 mm. within the next 10 days.[19, 20] At birth pulmonary artery pressures and aortic pressures are assumed to be equal,[21] but how long it takes for the aortic pressure to exceed the pulmonary pressure is not known. The assumption of a left-to-right shunt under suitable pressures presupposes the patency of the ductus arteriosus. It is not known definitely how long the ductus arteriosus remains open in the human newborn. In the fetal sheep functional closure of the ductus has been observed within five minutes after birth.[15] However more recently Dawes, Milne, Mott and Widdicombe[22] observed blood flows from the aorta into the pulmonary trunk in the newborn lamb which apparently lasted for several hours after delivery. They also observed closing of the valve of the foramen ovale within one to two minutes after the onset of breathing. These authors used cineangiography following injection of 70 per cent Thorotrast into the aortic arch. From our findings it seems very likely that the ductus arteriosus remains open also in newborn infants for varying periods after birth. The exact time of closure probably varies in different infants, but we have not found left-to-right shunt curves in infants older than 15 hours. Whether a reversal of shunt through the ductus arteriosus can occur in some infants under conditions of a higher pulmonary artery than aortic pressure cannot be stated with certainty. The peculiar diphasic curves found in some infants both younger and older than 15 hours could be the result of a right-to-left shunt through the ductus arteriosus. Eldridge, Hultgren and Wigmore[23] measured the oxygen content and capacity of capillary blood samples obtained from the previously warmed right hand and foot of 27 normal newborn infants during the first five days of life. The Roughton-Scholander microtechnic was used. They found that 9 of 11 infants 1 to 3 hours old had a significantly lower oxygen saturation in the foot than in the hand. In infants between 3 and 72 hours of age 5 of 10 cases showed a similar difference in oxygen saturation, but in those older than 3 days no difference was observed. They explained these findings on the basis of a veno-arterial shunt through a patent ductus arteriosus. These observations support the view that the diphasic curves probably represent a right-to-left shunt through the ductus arteriosus. More study with better methods is needed to determine more accurately the time of closure of the various fetal pathways.

In regard to cardiac output and cardiac index, the modified dye dilution method is relatively easy to use in small infants and the results obtained seem fairly accurate. This method has made it possible for the first time to measure the cardiac output of healthy newborn infants.

CONCLUSIONS

Newborn infants over 15 hours of age have a tendency to show dye dilution curves of

normal contour following the injection of a measured amount of T-1824 dye into the umbilical vein. Below this age a large percentage of infants have curves of abnormal contour, generally one of two types: either a left-to-right shunt type or a diphasic type. The most likely explanation for the former is a left-to-right shunt through the ductus arteriosus which has not yet closed. The latter type may be explained by a shunt reversal through the ductus arteriosus. Patency of the foramen ovale apparently is not concerned in the production of abnormal dye curves in the newborn infant under conditions of sleep.

Cardiac output has been satisfactorily determined by a modified dye dilution method which has been discussed in detail. The mean cardiac output value of 540 cc. per minute comes close to values estimated by a number of investigators on the basis of theoretical considerations.

Summario in Interlingua

Le curvas del dilution de colorantes e le rendimento cardiac esseva studiate in 29 neonatos de bon sanitate durante le prime 26 horas de lor vita. Esseva usate le methodo de Wood e socios. Trenta-sex pro cento del infantes studiate habeva curvas de contorno normal. In le majoritate de iste casos le infantes esseva plus que 15 horas de etate. Infra le etate de 15 horas le infantes tendeva a haber curvas de forma anormal. Istos esseva o diphasic o resimilava curvas del typo associate con derivation ab le sinistra verso le dextera. Il es probabile que illos esseva causate per un patente ducto arteriose. Le rendimento cardiac median esseva 540 cc per minuta.

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Atherosclerosis and Thrombosis of the Distal Part of the Abdominal Aorta

Clinical and Surgical Considerations

By JOHN W. KIRKLIN, M.D., EDGAR V. ALLEN, M.D., HOWARD M. ODEL, M.D., AND RICHARD M. SHICK, M.D.

DR. ALLEN: Partial or complete occlusion of the distal part of the abdominal aorta is characterized clinically by distress produced only by walking and relieved by standing. The amount of walking required to produce distress varies from patient to patient as well as from time to time in the same patient. Characteristically the distress involves the thighs, the regions lateral to the hip joints, the buttocks or, rarely, the distal part of the midlumbar zone. The onset of distress is accelerated when the patient walks up an incline or stairs, or when he walks rapidly. This symptom complex is recognized as intermittent claudication. It differs from that ordinarily noted in association with chronic occlusive arterial diseases involving the legs only in that its location is more proximal; it is commonly designated as "high" intermittent claudication. In rare instances, similar distress is produced in addition by standing or by exercise while standing, such as making beds or scooping grain.

PRESENTATION OF CASES

Case 1. (Presented by Dr. Allen.) A 43-year-old woman examined at the Mayo Clinic in May, 1954, had noted inconstant paresthesia in the entire lower extremities for several years. For the past two years she had noted distress involving the entire left lower extremity and the left buttock and lesser distress in the right buttock provoked by continuous walking and relieved by cessation of walking.

General examination disclosed no abnormalities except those relative to the arterial circulation of the lower extremities. Slight diminution of pulsation was noted in the right femoral artery, with pronounced diminution of pulsation of the left femoral artery. Faint pulsation was detectable in both popliteal arteries but no pulsation could be felt in the dorsalis pedis arteries bilaterally and in the left posterior tibial artery. Only slight diminution in pulsation was present in the right posterior tibial artery. On elevation of the feet, a minimal degree of abnormal pallor of the skin of both feet was noted. The venous filling time of the right foot was 25 seconds and that of the left foot was 35 seconds. A systolic bruit was audible over both femoral arteries.

Results of the following procedures were normal: urinalysis, enumeration of erythrocytes and leukocytes, serologic test for syphilis and roentgenologic examination of the thorax. Values for blood urea, sugar and hemoglobin were normal. Values for blood fats, expressed in milligrams per 100 ml. were: cholesterol 293, cholesterol esters 130, phospholipides 320 and fatty acids 492. Roentgenologic examination of the abdomen showed calcification of the abdominal aorta. Aortography disclosed a filling defect in the terminal portion of the aorta; the iliac and femoral arteries filled normally.

A diagnosis was made of atheromatosis and thrombosis of the distal portion of the abdominal aorta and surgical treatment was advised. Dr. Kirklin, will you discuss the operative procedure?

Dr. Kirklin: The aorta appeared normal proximal to the level of the origin of the inferior mesenteric artery. Distal to that point it was severely sclerotic and just proximal to its bifurcation the aorta was "solid" and appeared to be almost completely occluded. The left common iliac artery was normal to palpation but the proximal portion of the right com-

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The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

mon iliac artery was involved with atheromatosis. The external iliac arteries were normal to palpation.

The terminal portion of the aorta was mobilized; one lumbar artery and the inferior mesenteric artery were ligated and divided. A fine-toothed clamp of the Potts type was placed on the aorta about 2.5 cm. distal to the left renal vein and about 2.5 cm. proximal to the origin of the inferior mesenteric artery. Bulldog clamps were placed on the iliac arteries. The aorta was cut across about 1 cm. proximal to the origin of the inferior mesenteric artery. The common iliac arteries were sectioned and the aorta and proximal portions of the common iliac arteries were removed. A graft, comprised of the distal portion of an aorta, its bifurcation and the common iliac arteries, was inserted. At the conclusion of the operation excellent pulsation was detectable in both external iliac arteries. Lumbar sympathectomy was performed.

Pathologic examination of the surgical specimen showed that the distal 2 cm. of the aortic lumen was virtually completely obstructed by a nodular atheromatous mass. Atheromatous plaques were noted in the aorta and common iliac arteries; one plaque obstructed the orifice of the inferior mesenteric artery.

Dr. Allen: Much more occlusion of the aorta was found than was anticipated from study of the aortograms. Would you comment on this discrepancy, Dr. Kirklin?

Dr. Kirklin: Similar observations have been made in other cases in which the obstruction in the aorta demonstrated on direct examination was considerably greater than that assumed to be present as a result of aortography.

Dr. Allen: When the patient was examined 17 days after operation, pulsation in the peripheral arteries was normal, there was no abnormal pallor on elevation of the feet and the venous filling time of the feet was normal bilaterally. Relative to the surgical results, the patient wrote as follows: "One of the most noticeable changes since my operation is that I can walk without pain. The day after I was released from the hospital I walked 10 blocks and went through several stores without having to stop and rest because of pain, fatigue, dizziness or just plain inability to put one foot ahead of the other. Prior to operation I could walk a half block or possibly up to one block and then had to stop and rest for a few minutes until the pain and fatigue would leave, then start again only to repeat this procedure. Walking up a flight of stairs was a major job. I have had occasion to climb a flight of stairs since the operation with no noticeable strain on my legs. I am now lifting my feet instead of dragging them. For several years my feet and legs have always felt cold and if I became chilled it was most difficult to get my legs and feet warm even with the aid of hot baths, a heating pad and an electric blanket. Now I definitely have "hot" feet; in fact I feel a warmth all through my body that I never experienced before—really a little too warm. A cool morning breeze feels delightful now instead of creating shivers and goose pimples from head to toe. I just hope it continues."

Case 2. (Presented by Dr. Odel.) A research chemist, 53 years of age, registered at the clinic in March, 1954. He described gradually progressive "tiredness" in both legs and thighs that invariably occurred after he walked one block at a moderate pace; the distress increased with continuous walking and required him to stop. It then disappeared but recurred when he walked again. The clinical history was otherwise negative except for inability to have penile erection for two years.

General examination disclosed extensive xanthomas of both upper eyelids. Arterial pulsation was greatly diminished in both femoral arteries and slightly diminished in the left posterior tibial artery; it was absent in both popliteal and dorsalis pedis arteries and in the right posterior tibial artery. Elevation of both lower extremities produced mild abnormal pallor of the right foot but none on the left. With dependency, venous filling occurred normally.

Results of the following tests were normal: urinalysis, enumeration of erythrocytes and leukocytes, and serologic test for syphilis. Values for blood sugar and hemoglobin were normal. The respective values for blood cholesterol, phospholipides and fatty acids in milligrams per 100 ml. were 420, 570 and 1,674.

A provisional diagnosis was made of arteriosclerosis obliterans, with the occlusive process in the iliac arteries or in the aorta itself or in both. Aortography revealed irregularity and narrowing of the abdominal aorta beginning distad to the renal arteries and including the proximal portions of both common iliac arteries. The distal portions of the iliac and the femoral arteries were filled normally (fig. 1, *A* and *B*). A diagnosis then was made of atheromatosis with segmental occlusion of the distal portion of the abdominal aorta and the common iliac arteries. Surgical treatment was advised.

Dr. Kirklin: The abdominal aorta and common iliac arteries were exposed through a midline incision. Pulsation appeared normal in the aorta to within 1 cm. of the bifurcation, where it abruptly became of poor quality. Direct recording of blood pressure in the aorta was done at points 8, 6, 4 and 2 cm. proximal to the bifurcation; the values obtained were approximately the same as in a radial artery, namely 160 mm. Hg systolic and 90 diastolic. The blood pressure in the common iliac arteries just distal to the bifurcation of the aorta was 125/90 on the right and 114/90 on the left. These readings indicated sharp reduction of the systolic blood pressure owing to the damping effect of the obstruction at the bifurcation of the aorta. The aorta was me-

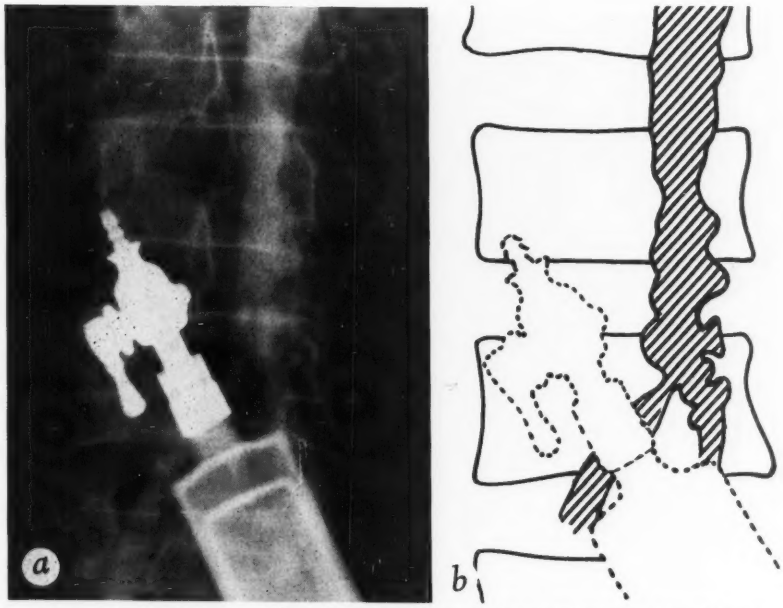

FIG. 1 (case 2). *A*. Aortogram. Note irregular filling of the distal part of the abdominal aorta. The right common iliac artery is severely occluded at the point of origin; the lumen of the left common iliac artery is narrowed. *B*. Drawing of same aortogram.

bilized and, after placement of suitable fine-toothed clamps, was cut across just below the origin of the inferior mesenteric artery. The distal part of the aorta and the first centimeter of each iliac artery were then removed. The inferior mesenteric artery was temporarily occluded with a bulldog clamp. A preserved homologous bifurcation graft was sutured into place. Pulsation through the graft and into the iliac arteries appeared to be good at the conclusion of the operation. The second lumbar sympathetic ganglion on the right and the second and third ganglia on the left were removed. Pathologic study of the specimen showed extensive atherosclerosis of the aorta with an organized thrombus, approximately 1.5 cm. in diameter, situated at the aortic bifurcation and virtually obstructing the lumen.

Dr. Odel: When the patient was examined about two weeks after operation, peripheral arterial pulsation was normal or nearly so in the femoral, popliteal and posterior tibial arteries bilaterally. Faint pulsation was present in the dorsalis pedis arteries bilaterally. There was no abnormality of pallor on elevation of the feet, and the venous filling time was normal. The patient recently wrote, "My walking pains have never appeared again. However, there are still some kind of drawing pains in my right leg even when I am not walking."

Case 3. (Presented by Dr. Shick.) A 45-year-old white man was admitted to the clinic in April, 1954, complaining of pain in both hips and calves and impotence of 18 months' duration. The symptoms had begun insidiously and had become progressively worse. Pain appeared after the patient walked one and a half or two blocks and subsided after he rested for a few minutes. He had smoked excessively for several years but recently had discontinued use of tobacco on the advice of his physician.

Results of general examination were not remarkable except that the feet were cool and evidenced slight abnormal pallor on elevation. Filling of the veins in the left foot was slightly delayed after the extremities were changed from an elevated to a dependent position. Pulsation was felt in the abdominal aorta. Arterial pulsation was palpable in the femoral, popliteal, dorsalis pedis and posterior tibial arteries but was moderately to greatly impaired. A systolic bruit of moderate intensity was audible over the right femoral artery.

Urinalysis revealed moderate albuminuria. Aortography showed partial obstruction at the aortic bifurcation (fig. 2). The results of other studies, including measurement of blood hemoglobin, sugar, urea and lipides, enumeration of erythrocytes and leukocytes, roentgenography of the thorax and excretory urography, were normal. Roentgenograms of the abdomen and pelvis revealed no calcification in the abdominal aorta or iliac vessels. The clinical diagnosis was atheromatosis and thrombosis at the aortic bifurcation. Surgical treatment was advised.

Dr. Kirklin: Surgical exploration in June, 1954,

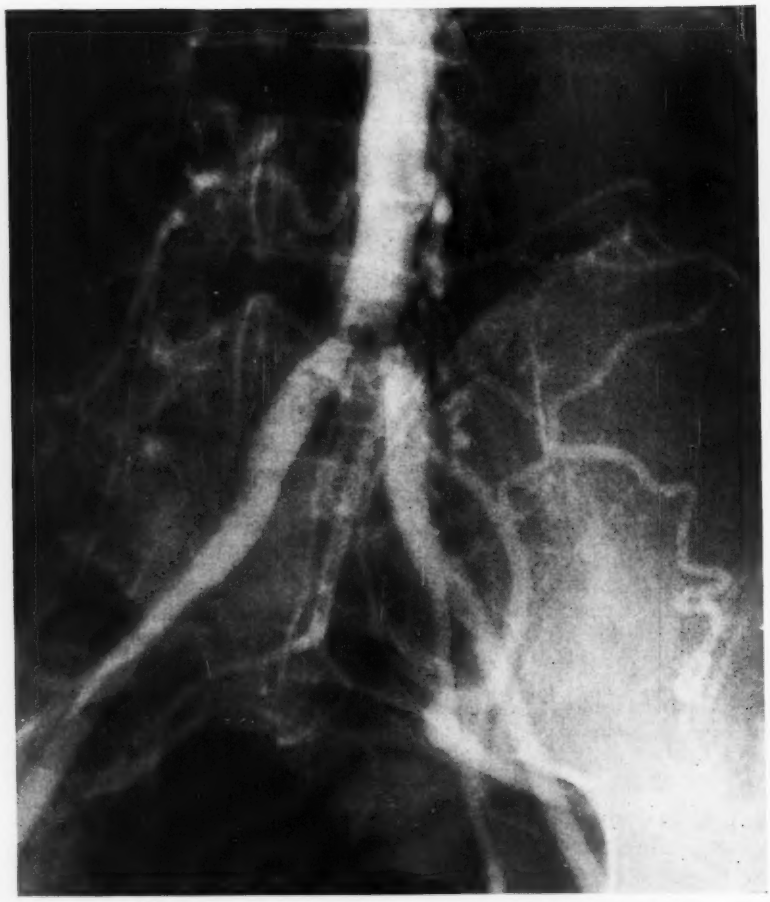

FIG. 2 (case 3). Preoperative aortogram. The lumina of both common iliac arteries at their origin are greatly narrowed; there is incomplete filling of the distal portion of the abdominal aorta.

disclosed good pulsation in the abdominal aorta down to the actual point of its bifurcation. Beyond this in each common iliac artery the pulsation was greatly diminished. Minimal atherosclerosis was present in the aorta and iliac arteries above and below the involved segment. The distal 3 cm. of the abdominal aorta and the proximal 3 cm. of each common iliac artery were resected and continuity was restored by means of a Y-shaped homologous aortic graft. Bilateral lumbar sympathectomy was done. Immediately after the operation it was noted that the lower extremities were warmer than they had been and that the arterial pulsation was of good quality. Convalescence was uneventful and the patient was dismissed from the hospital on the tenth postoperative day.

Dr. Shick: The patient returned to the clinic in October, 1954, stating that he was able to walk more than a mile without distress and to obtain and maintain penile erection without difficulty. The lower extremities were warm and dry. No abnormal postural changes in color of the skin of the feet were noted and filling of the veins was prompt after the limbs were changed from an elevated to a dependent position. Pulsation was felt in the abdominal aorta; no bruit was audible. Arterial pulsation in the lower extremities was normal. Aortography revealed the aortic bifurcation to be well filled and normal in size (fig. 3).

COMMENT

Dr. Allen: The results of operation in these three cases were excellent, as they have been in several similar instances. However, surgical results are not uniformly good and it is well to

FIG. 3. (case 3). Postoperative aortogram. The lumina of both common iliac arteries and the distal portion of the abdominal aorta are filled normally.

consider the important factors common to these three cases, which are as follows: 1. The history in each case was that of "high" claudication, in which the distress provoked by walking involved the thighs or the hips; in other cases it has involved the buttocks. 2. Minimal evidence of ischemia of the feet was noted, as shown by the absence of much abnormal pallor on elevation of the lower extremities and by the presence of normal or nearly normal venous filling time. 3. Aortography disclosed patency of the distal part of the iliac arteries and the femoral arteries.

The observations relative to these three cases will not pertain to all cases of aortic thrombosis, for this condition may be part of diffuse arterial disease with arterial thrombosis in the arteries of the legs. Dr. Kirklin, would you discuss your experience with this situation?

Dr. Kirklin: During early experience with aortic thrombosis, an occluded distal portion of the abdominal aorta and the common iliac arteries were resected and replaced with a graft, even though the distal portions of the iliac arteries were occluded. The occluding masses were "fished out" of the interior of these distal arteries prior to anastomosis. The patients derived no benefit from this procedure. It might be argued that the resection was not carried far enough distad but it was impossible to resect entirely past the occluded region, which extended at least as far down as the inguinal ligaments. It is probably fruitless to perform resection under such circumstances. My colleagues and I are still gaining experience in the indications for resection of the abdominal aorta for thrombosis and replacement with a graft, and our ideas are not entirely crystallized relative to some aspects. For example, I do not know how much can be gained from such an operation when the aorta is occluded, the iliac arteries are patent and the more distal parts of the arteries are occluded.

Dr. Allen: Sometimes the roentgenograms do not show filling of the iliac and femoral arteries when clinically they appear to be patent, although they are pulseless because pulsation has been damped by occlusion in the aorta. How do you handle such a situation, Dr. Kirklin?

Dr. Kirklin: We have operated in such cases. Resection and grafting have been done if the distal portions of the iliac arteries were found to be patent. If the arteries are occluded as far distad as the inguinal ligaments, bilateral lumbar sympathectomy only has been performed.

Dr. Odel: Do you believe, Dr. Kirklin, that sympathectomy alone could account for the good results in the three cases that we have reported?

Dr. Kirklin: It has been known for many years that sympathectomy improves arterial circulation to the skin of the extremities. However, our experiences indicate that sympathectomy alone does not cause the improvement noted in these three cases.

Dr. Allen: I agree. Most patients cannot walk farther after sympathectomy than they could before. Complete relief of intermittent claudication after sympathectomy must be extremely rare; I cannot remember such an instance. Also sympathectomy rarely causes an increase in arterial pulsation. It is safe to

conclude that removal of the diseased aorta was responsible for the relief of intermittent claudication and for most of the improvement in arterial circulation in these cases.

Physician: Why do you do sympathectomy, Dr. Kirklin?

Dr. Kirklin: Even in carefully selected patients there may be impoverishment of the circulation to the feet that will not be benefited by resection and replacement of the aorta only. Sympathectomy may cause substantial improvement in circulation. Also sympathectomy is performed to prevent, in some degree, the ischemia that may develop subsequently owing to atherosclerosis and thrombosis of arteries in the legs.

Dr. Shick: Dr. Kirklin, what do you do when aortography demonstrates occlusion of the aorta as far proximad as the origin of the renal arteries? Can you make an anastomosis under those circumstances?

Dr. Kirklin: Fortunately we are not confronted often with such a situation. Yet it is possible to remove a thrombus from the aorta just distal to the origin of the renal arteries and then complete the operation in the usual way. This was done in a recent case in which the atheromatous occlusion extended to within 1.5 cm. of the derivation of the renal arteries. The portion of aorta between this point and the origin of the renal arteries was pulseless and contained a soft mass. A clamp was placed across the aorta about 1 cm. distal to the renal arteries and the aorta was transected about 0.5 cm. beyond the clamp. The bit of aorta extruding beyond the clamp had a normal-appearing wall but was occluded by a soft organized thrombus that was separated readily from the intima of the aorta. The thrombus was grasped with forceps and the clamp was loosened; traction on the thrombus in addition to the pressure within the proximal part of the aorta produced forceful dislodgment of the thrombus from the segment of aorta between the origin of the renal arteries and the point of transection. The clamp was quickly tightened and the operation concluded in the usual way.

Physician: What about thromboendarterectomy?

Dr. Kirklin: Some surgeons prefer this operation to resection and grafting. We performed thromboendarterectomy on several patients before we began to perform resection and grafting; pulsation returned to the arteries of the legs of two such patients. One of these patients died two and one half months later of rupture of the aorta near the proximal end of the region of the thromboendarterectomy, although reinforcement of the aorta with fascia had been employed at the time of operation. Because of this experience and because of certain theoretic disadvantages to thromboendarterectomy, my colleagues and I prefer resection and grafting at present.

Physician: What happens to the graft?

Dr. Kirklin: The considerable amount of experimental work done on the fate of preserved homologous aortic grafts can be summarized by saying that, in general, the graft serves essentially as an inert scaffold for the ingrowth of specialized tissues from the host. In time the graft is replaced by the tissues of the host and does not persist as a transplanted structure.

Physician: Are the results good when an iliac artery is resected for segmental occlusion and replaced by a graft?

Dr. Kirklin: Investigation of this problem is being continued but, for reasons not currently clear, substantial improvement in circulation has not often occurred after operation in our cases of isolated segmental occlusion of the common iliac arteries. The small size of the common iliac artery may have some bearing.

Physician: At a conference some time ago Dr. Allen mentioned arteriospastic claudication. Does that situation apply in cases such as those presented?

Dr. Allen: For several years my associates and I have been intrigued by the following situation. A patient has well-documented intermittent claudication, yet pulsation in the peripheral arteries is normal. After exercise, such as walking or rising repeatedly on the toes, arterial pulses of the feet disappear, the veins of the feet are empty and collapsed and the skin of the distal portions of the feet is pallid. At this time a systolic bruit may be heard for the first time over the femoral arteries or a bruit previously audible may be

harply accentuated. This is the syndrome of rteriospastic claudication, which we have bserved to occur on occasion with aortic hrombosis, as well as in the absence of aortic hrombosis but with segmental occlusion of the iac or femoral arteries. I cannot be entirely ertain that arteriospastic claudication is an nequivocal sign of segmental arterial occlusion ut it well may be because the two are com- nonly associated.

Physician: What is the mortality rate?

Dr. Kirklin: We have performed resection nd grafting for acquired occlusion of the bdominal aorta in 18 cases; there have been o deaths and no serious complications.

Physician: Are patients satisfied with the results of operation?

Dr. Allen: Very much so. Several patients have written to express gratitude and great satisfaction with the results of operation. As far as I know, none regret the experience if the results have been good. They have not lamented the pain, loss of time and expense of operation. One patient wrote: "I feel like I am floating on a cloud—I feel much younger." However, none of us are naïve enough to believe that the surgeon is curing atherosclerosis. He is removing atheromatous and thrombosed arteries and replacing the defect with a graft. Atheromatosis certainly is present in other regions when it is found in the aorta. Therefore, one may anticipate the normal consequences of atheromatosis whatever they may be and whenever they may occur. We will need much more time than we have had to determine the incidence and severity of impoverished circulation to the legs that may result from atherosclerosis in the arteries of the legs.

The current situation may be summarized as follows: The syndrome of occlusion of the distal portion of the abdominal aorta or the segments of the iliac arteries or both may be recognized clinically. Demonstration of details depends on aortography. The distal part of the abdominal aorta or portions of the iliac arteries or both may be removed surgically and replaced by a homologous graft. The risk of operation to the patient is minimal. When operation is performed on carefully selected patients, the results are extremely pleasing to patient, surgeon and internist.

CLINICAL PROGRESS

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Intermittent Claudication

By STANFORD WESSLER, M.D.

INTERMITTENT claudication occurs most frequently in the lower extremities although other muscle groups are not immune. The diagnosis of intermittent claudication is acceptable when physical exertion produces pain or paresthesias in the foot, calf or thigh, promptly relieved by the cessation of the activity without change of position of the affected part. It never occurs in the legs as a result of standing, reclining or sitting and it has no relationship to the muscle cramps which patients have in bed.

Many diseases may affect the peripheral arteries and produce intermittent claudication. Thromboembolic obstruction, thromboangiitis obliterans, polyarteritis nodosa, scleroderma, and the arteritis associated with systemic infection may be encountered. Atheromatosis, with its predilection for the major arteries of the lower leg is the most common cause of intermittent claudication. The disturbance in function, however, is primarily dependent upon the location, extent and rate of development of the arterial obstruction rather than its specific etiology.

MECHANISM

It is now generally accepted that intermittent claudication results from muscular ischemia secondary to arterial occlusive disease when blood supply is adequate for resting muscle but inadequate for a muscle which is actively contracting. The precise metabolic disturbance initiating the syndrome has, however, never been fully elucidated. The oxygen requirement of contracting muscle may increase 30 times above the resting level. This vastly increased requirement is met in part by extraction of more oxygen from each unit of blood passing through the capillaries and in part by an increase in arterial and capillary blood flow. It is the inability of obstructed arteries to deliver this additional blood that produces intermittent claudication.

Some investigators have maintained that arterial spasm alone can produce claudication. Support for this point of view has centered around the observation that there is often a diminution in the peripheral pulses after exercise in patients with intermittent claudication in whom pedal pulses were palpable at rest. Others have not found the evidence for spasm at all convincing. Pickering[1] has shown how closely organic vascular narrowing and occlusion may mimic vascular spasm. The two known stimuli producing spasm are trauma and cold. While any artery adequately stimulated mechanically will probably go into spasm, there are no documented cases of intermittent claudication occurring from spasm alone. Thus, in Raynaud's phenomenon, although an intrinsic inherited peculiarity causes the digital arteries to respond to cold with intense constriction, intermittent claudication is not seen.

The neurogenic aspect of intermittent claudication has been extensively studied. The sensory and motor changes developing during a period of circulatory arrest to a limb have been described. Marked sensory impairment has always been noted long before any pe-

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ceptible deterioration in motor power. In a recent investigation of the effect of peripheral ischemia on nerve conduction, it was shown that among afferent fibers, the more rapid the conduction velocity of the fiber, the greater the depressant effect of ischemia. Motor fibers, however, are more resistant to ischemia than certain afferent fibers of slower conduction rate. The different sensitivities of nerve fibers to ischemia may explain why pain precedes loss of motor power and why, under some circumstances, intermittent claudication may be experienced as a pain and at other times as a paresthesia.

Diagnosis

In the vast majority of patients with claudication the pedal pulses are absent. So constant is this finding that one should be extremely hesitant, in the absence of anemia, to entertain a diagnosis of claudication if both the dorsalis pedis and posterior tibial pulses are full and bounding. Intermittent claudication has probably escaped recognition in severe anemia because it is usually a minor complaint and one that is likely to be grouped among the paresthesias commonly found in anemic patients.

Occasionally, normal peripheral arterial pulsations may not be palpable because the vessels pursue anomalous pathways. It is clear, however, that a considerable degree of narrowing and even occlusion can be present in the large arteries without producing detectable reduction in arterial pulsation. The brief course and large diameter of some collateral branches that bypass short occlusions explain the frequent clinical finding of the return of pulsatile flow distal to a complete occlusion (fig. 1). In such cases one does not expect, and one does not usually find, evidence of ischemia. If a patient complains of pain in the leg and the arterial pulsations are full and bounding, the symptom almost certainly is not due to arterial insufficiency.

Claudication in patients with normal or only partially impaired peripheral arterial pulsations has been attributed to occlusions of the branch arteries supplying important muscle groups and also to arteriolar obstruction. Patients in whom pedal pulses were present have been observed with claudication secondary to occlusion of an iliac artery or to coarctation of the aorta. In coarctation the velocity of blood flow in the large arteries of the leg is reduced, and the arterial-arteriolar difference in blood pressure greatly diminished. This small arterial-arteriolar difference represents sufficient encroachment on the local circulatory reserve to produce ischemic pain without obliterating the pulse. In the occasional patient with claudication and palpable pedal pulsations the occlusion will frequently be found proximal to the femoral artery. In view of the demonstrated occurrence in peripheral atherosclerosis of obstruction of the large arteries and the development of a rich collateral circulation, which could occasionally permit pulsatile flow distal to the occluded area, this explanation (i.e. occlusion proximal to the femoral artery) appears more reasonable than one that postulates small-vessel obstruction as the sole mechanism for claudication.

The clinical picture of intermittent claudication is frequently complicated by the coexistence of other pathologic conditions, such as neuritis or arthritis, that may cause pain in

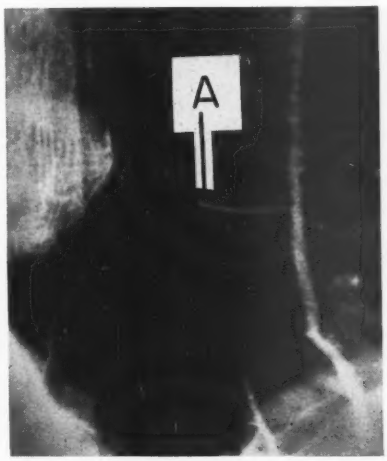

Fig. 1. Roentgenogram of an amputated limb after injecting the arteries with radiopaque medium. "A" indicates an anastomotic vessel between the calcified but patent anterior tibial artery and the peroneal artery. The internal diameter of the collateral channel exceeds that of the main peroneal artery.

an extremity. It is important routinely to consider the existence of these other lesions since the symptoms they produce may be more disabling than the claudication itself. In most instances a careful history and physical examination will clarify the problem.

Value of Oscillometry, Arterial Calcification and Arteriography

The oscillometer remains overrated as an aid in estimating the degree of arterial insufficiency. The impression that it is more accurate than palpation undoubtedly derives from its graphic representation of the arterial pulse. The normal range of values is extremely broad and is influenced by the diameter of the extremity as well as by the manner of application of the pneumatic cuff. The limitations of the instrument are emphasized by situations in which the arterial circulation is excellent and yet the oscillometric excursion small. Occasionally, careful palpation reveals pulsations which are not recorded by the oscillometer. The instrument has its main value in confirming the absence of palpable pulses and in demonstrating a difference in pulsatile flow in the two extremities when peripheral pulses cannot be discerned. It is, however, essential to realize that oscillometric readings do not accurately reflect the effectiveness of the collateral blood supply.

In the past, undue significance has been attached to the presence of calcification in the walls of atherosclerotic vessels. The clinical effects of atherosclerosis are not dependent so much on hardening of the vessels as on narrowing or obliteration of the lumen. Calcification is not only inconstant but also is a relatively benign process, causing little if any interference with the flow of blood. Of particular interest are several reports of the lack of correlation between arterial calcification and occlusion and even of an inverse relation between the two. A recent study has clearly demonstrated the absence of any correlation between calcification and occlusion in patients in whom

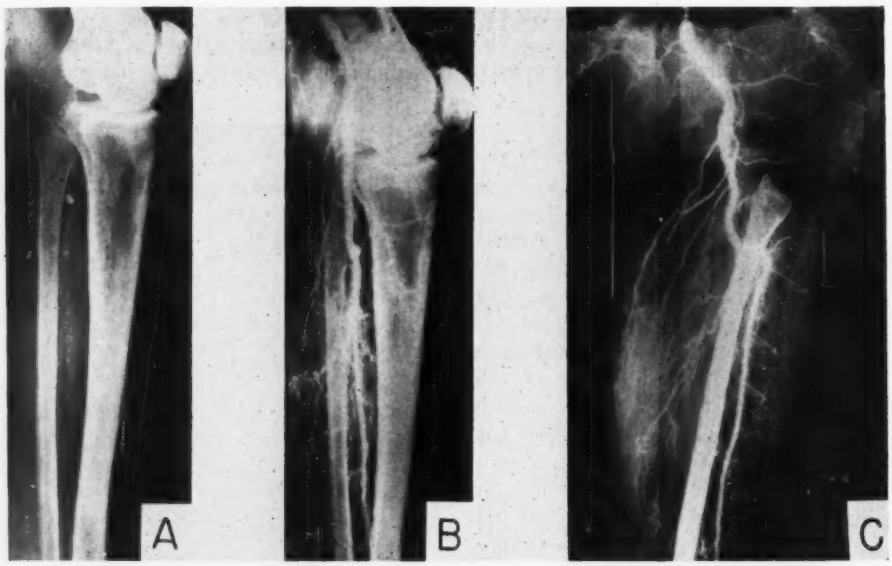

FIG. 2. Roentgenogram of amputated leg showing inverse relation between arterial calcification and occlusion. A: Lateral roentgenogram prior to arterial injection of radiopaque medium. Visible calcification of entire popliteal and anterior tibial arteries and upper fourth of posterior tibial artery. B: Lateral roentgenogram after injection. Popliteal, anterior tibial and upper fourth of posterior tibial arteries patent. Occlusion of remainder of posterior tibial and all of peroneal arteries. C: Roentgenogram of leg after it has been "unrolled" so that major vessels lay in one plane. Sites of patency and occlusion shown more clearly than in B.

the clinical picture of atherosclerosis and gangrene was sufficiently severe to necessitate amputation[2] (fig. 2). These observations indicate that the taking of a roentgenogram merely to determine whether or not arterial calcification is present does not contribute materially to the diagnosis of intermittent claudication.

Since it is easy to demonstrate collateral vessels by the injection of radiopaque mediums during life it was natural that arteriography should be employed in the evaluation of patients with intermittent claudication. It has not been possible, however, to translate these objective anatomic evidences of collateral flow into functional terms. Arteriography, thus, cannot be used as a prognostic guide to therapy or as an indication of the paucity, richness or effectiveness of these auxillary vessels. One does not need an arteriogram to appreciate that collateral circulation must be extensive if major arterial pulsations in the limb are absent and the tissues of the toes are viable.

It should be realized that, although occlusions are not rare in the femoral and iliac arteries, the most frequent site of obstruction in atherosclerosis is between the knee and the ankle.[2] It is precisely this bottleneck area that is most difficult to visualize completely even with a good contrast medium. It is much easier both during life and at necropsy to demonstrate the femoral artery, the popliteal artery or the terminations of the anterior and posterior tibial arteries in the foot than to visualize the tibial arteries in the lower leg. The intra-arterial injection of radiopaque mediums, moreover, is not performed without discomfort or risk. Arteriography is a valuable diagnostic aid in reconstructive surgical procedures on obstructed arteries. Knowledge of the localization of the occlusive process and the limits of arteriography should, however, temper any surgical plan to relieve intermittent claudication in the atherosclerotic limb by restoring the integrity of the arterial lumen in the thigh.

Therapy

To provide effective therapy for intermittent claudication, the physician must be cognizant of certain facts about the syndrome and of the patient's reaction to his disability. Spontaneous improvement in intermittent claudication shortly after its onset is frequently observed. Significant variations in exercise tolerance occur naturally in the course of the disease. After occlusion of a major artery in an extremity, one may expect an increase in collateral circulation during the first year: this increase may continue for two or three years, independent of therapy.

The initial distress of the patient with intermittent claudication is often out of all proportion to the actual disability. This discrepancy is due, in some cases, to the fact that the syndrome represents the first serious physical impairment encountered in a vigorous, active life and one that is envisaged as becoming inexorably more confining as time passes. Others interpret "hardening" of the leg arteries to mean the inevitable spread of vascular disease to other vital organs. Finally, there are those who equate intermittent claudication with gangrene and amputation. The physician who fully appreciates such fears is in an excellent position to help these patients.

In practice, the disability in most patients with intermittent claudication is not profound; only a small percentage have to change their employment because of a limited exercise tolerance. Furthermore, intermittent claudication does not have the same prognostic relation to gangrene and amputation that angina pectoris has to death from myocardial infarction, cardiac arrhythmia or congestive heart failure.

In this clinical setting therapeutic attempts to alleviate claudication should be essentially devoid of risk. In addition, all measures aimed at relieving intermittent claudication should have as their goal a decrease in the disparity between the supply and demand for blood by ischemic tissue. Any procedure diverging from this aim may aggravate the disability.

Today there is no single, effective measure for the treatment of intermittent claudication that has gained wide acceptance. This is not for any lack of ingenuity on the part of workers in the field. Within the last half-century many diverse therapies have been suggested. Drugs investigated have included calcium, vitamin E, theobromine, methyl testosterone, depropanex,

cytochrome C, intravenous hypertonic saline solution, thiouracil, histamine and various sympatholytic agents.

Mechanical aids, some of them based on demonstrably favorable physiologic alterations in peripheral blood flow, have included intermittent venous occlusion, passive vascular exercise (Pavaex) and Buerger's exercises.

Surgical procedures have also covered a wide spectrum. It has been recommended that the femoral vein be ligated, and that the femoral artery be anastomosed to the femoral vein. More recently, accessible occluded femoral and popliteal segments have been resected and replaced by grafts. In addition to this direct attack on the blood vessels themselves, the sympathetic innervation of the lower extremity has been interrupted by periarterial stripping, paravertebral blockade with procaine, alcohol and phenol and extirpation of the lumbar ganglions. Finally, division of the common peroneal and posterior tibial nerves and tenotomy of the Achilles tendon have been attempted.

Much interest exists in the therapeutic value of interrupting sympathetic tone either medically or surgically in intermittent claudication. Although there is little evidence that the arteriolar vessels are in spasm in intermittent claudication, it has been assumed that dilatation of the arteriolar and postarteriolar bed will improve the nutrition of ischemic tissue. Unfortunately, methods such as measurement of skin temperature and limb volume changes do not record effective capillary blood flow but rather increments in the total amount of blood or the rate at which blood passes through a portion of the extremity. There is evidence that sympathetic denervation produces a relaxation of the direct arteriovenous communications as well as of the arteriole-metarteriole-capillary network. Whether it is possible, therefore, to improve capillary blood flow by removing normal tone is not at all clear. The observation that interruption of sympathetic activity may increase skin temperatures does not necessarily imply a similar vasodilatation in deep structures. The reverse has in fact been claimed. Some observers believe that interruption of normal sympathetic tone (even without producing systemic hypotension) may occasionally aggravate ischemia. Although secondary arterial and venous thrombosis has been implicated, the mechanism whereby such a catastrophe could occur might be from extensive diversion of blood from ischemic tissue through dilated arteriovenous sluices.

Systemically administered vasodilators may cause vasodilatation throughout the body, thereby defeating their purpose. It is clear that there is a relatively greater "resistance" to the interruption of sympathetic tone in the lower as compared to the upper extremity. This resistance may require the use of relatively large dosages of sympatholytic agents with resulting hypotension and tachycardia. Among patients with coronary artery disease such disturbances in hemodynamics may precipitate myocardial ischemia and even necrosis. In this regard it is essential to recall the high incidence of coronary artery disease in patients past 50 years of age as well as the fact that many patients may have coronary artery obstruction without clinical manifestations. In the great majority of patients with intermittent claudication, therefore, the systemic use of vasodilator drugs is probably contraindicated.

There have been several reports of the value of intra-arterial vasodilators in the management of intermittent claudication. This route of administration, it has been claimed, will minimize the systemic effects of the drugs. Recently, however, the intra-arterial injection of Priscoline has also been reported to cause myocardial infarction. Intra-arterial therapy requiring repeated arterial puncture invites, of course, the risk of thrombosis in sclerotic arteries. The value of such treatment in patients with advanced obliterative disease remains to be established.

Surgical sympathetic denervation has been claimed to produce a "local" vasodilatation and a relief from the pain of claudication. Yet, lumbar sympathectomy causes a response not only in the ischemic area but throughout the entire extremity. As mentioned above, there is inadequate evidence that effective nutritional blood flow is increased by this pro-

cedure. Finally, experimental and clinical data indicate that in a large majority of patients, return of sympathetic tone occurs within months of the operative procedure, even though the foot may remain warm. These observations tend to invalidate the claim that sympathectomy has any "prophylactic" value in the prevention of intermittent claudication.

In patients with intermittent claudication and arteriographic evidence of a segmental occlusion in the femoral artery, resection of the occluded zone and its replacement with a venous or arterial graft has been recommended. Such a procedure, it has been argued with justification, would deliver blood to the tibial arteries at a more effective pressure. This potential advantage, however, must be balanced against the limited disability produced by the claudication and the multiple risks of the operative procedure itself. Segmental arterial resection for intermittent claudication remains an experimental procedure: it is our opinion that the underlying pathologic disturbance and the clinical course of the disability will ultimately cause this therapeutic approach to be discarded.

Tenotomy of the Achilles tendon is another procedure recommended for the relief of intermittent claudication. It is well established that uncomplicated claudication can invariably be relieved by a slowing of the rate at which the patient walks; tenotomy effectively achieves such a reduction in speed. However, it is usually possible to induce patients to walk more slowly without resorting to psychosurgery.

Despite the apparent therapeutic nihilism expressed in the preceding paragraphs, a detailed, concrete and positive program can be offered the patient suffering from intermittent claudication. On the basis of the pathologic physiology and the emotional responses referred to earlier in this presentation, every physician can effectively treat these patients without intricate diagnostic or therapeutic technics. The following description summarizes the approach currently used at the Beth Israel Hospital. Several illustrative cases are also included.

Practical Management of Intermittent Claudication

I. *Establishing the Diagnosis*

Many patients are referred with an incorrect diagnosis of claudication. It is important to remember that the diagnosis of claudication is made entirely by history; since the diagnosis carries considerable significance to the patient, it should not be accepted lightly. Fortunately, claudication is one of the most specific of symptoms. It is brought on only by continuous exercise and is relieved promptly by discontinuance of the exercise without change of position of the affected part. Furthermore, it is most unusual to be unable to demonstrate some impairment of the peripheral pulsations in these patients. Attention to these simple details will eliminate errors in diagnosis.

II. *Determining the Ancillary Factors*

Having established that intermittent claudication is present, one must next search for ancillary factors important in increasing the disparity between blood supply and demand. The most common of these are congestive failure, anemia, diabetes, and fresh arterial occlusion.

a. *Congestive Failure and Anemia.* The role of congestive heart failure and anemia in aggravating arterial insufficiency deserves special emphasis. Marked reduction in peripheral blood flow and vasoconstriction occur in advanced congestive heart failure. Reversal of these altered hemodynamics by successful treatment of the congestive heart failure is frequently accompanied by a decrease in the ischemia. In anemia the tissues are supplied with oxygen adequate for basal requirements, but the low tissue oxygen tensions result in a diminution of the margin of safety. Thus, in the presence of advanced occlusive disease, even a mild anemia may decrease this margin of safety sufficiently to tip the delicate balance between adequate nutrition and ischemia. Although it has been demonstrated that anemia may stimulate interarterial anastomoses; once clinical manifestations of claudication have developed in an extremity, ischemia will be decreased by cor-

rection rather than maintenance of the anemia. It is important, in this regard, to realize that the formed elements of the peripheral blood and bone marrow do not change strikingly as people grow older and that a mild anemia in elderly patients is not a "normal" finding.

b. *Diabetes.* The prominence of diabetes among patients with arterial occlusive disease and gangrene is impressive. If glucose tolerance curves are obtained on all patients with arterial occlusive disease and gangrene, the incidence of diabetes becomes even greater. The infrequency with which gangrene has developed in patients with normal glucose tolerance curves has been so striking among our patients with peripheral arterial obstruction that we have found this simple test to be of considerable value in predicting the clinical course of arterial insufficiency. The severity of the diabetic state is not related to the development of gangrene and in many patients the metabolic defect can be recognized only after examination of the blood sugar. Diabetes, therefore, should be suspected in every patient with peripheral atherosclerosis.

It is not difficult to understand why diabetes alters unfavorably the prognosis in intermittent claudication. The metabolic disorder probably accelerates the atherosclerotic process itself. It is, thus, associated not only with peripheral atherosclerosis but also with coronary atherosclerosis and resultant congestive heart failure. Diabetes produces retinal and peripheral neuropathy and accelerates cerebral atherosclerosis: the former impairs the patient's awareness of local trauma; the latter, with its attendant mental changes, interferes with the patient's ability to insure good care of his feet. Finally, resistance to infection may be impaired in diabetic patients.

c. *Fresh Arterial Occlusion.* A fresh embolic or thrombotic arterial occlusion may be associated with the onset of intermittent claudication or may cause a sudden decreased walking tolerance in patients with established claudication. Factors such as hypotension and polycythemia which favor the development of intravascular thrombosis therefore require prompt and effective correction. In every patient in whom a fresh arterial occlusion led to gangrene at the Beth Israel Hospital during the past five years, extensive propagation of the clot was found. Since one cannot predict in which patient extension of a fresh occlusion will occur, we have considered as medical emergencies all patients with fresh arterial occlusion and have treated them promptly with anticoagulant drugs.

At the present time an ideal anticoagulant is not available. There is some experimental and clinical evidence to indicate that substances such as Dicumarol which depress prothrombin conversion may not provide optimal anticoagulant activity. At present heparin is considered by us the drug of choice in the short-term treatment of acute arterial occlusion. Recently, a new method has been described for the intermittent intravenous administration of heparin without repeated venipunctures.[3] The technic is based on the use of inlying polyethylene catheters attached to rubbercapped Tuohy-Borst adapters. Catheters have remained in veins for as long as four weeks without the development of ascending thrombophlebitis or systemic reactions. The method has been used successfully in the prophylaxis and treatment of thromboembolism in patients with a variety of underlying pathologic states. Patients with acute myocardial infarction were treated with heparin without greater inconvenience than is incurred with Dicumarol controlled by a daily prothrombin time.

d. *Additional Factors.* With surprising frequency, patients with claudication are more seriously disabled by an unrecognized coexisting disability than by their arterial insufficiency. Night cramps abolished by quinine or pyribenzamine, flat feet corrected by arch supports, the postphlebitic syndrome ameliorated by elastic bandages, chronic gouty arthritis relieved by uricosuric agents may so improve a patient's walking tolerance that the discomfort from the claudication alone is no longer disabling. If some such ancillary disability is diligently searched for in each patient with claudication, the therapeutic yield will be very gratifying.

A positive program also requires a re-evaluation of the medical profession's attitude concerning smoking. The continued use o

tobacco by patients with intermittent claudication is still strongly interdicted by many authorities. The fact that tobacco smoking increases the tone of peripheral vessels is adequate justification for urging all patients with acute arterial insufficiency to stop smoking, at least until the imbalance between obstruction and collateral flow has been improved. It is equally justifiable on the basis of a substantial body of clinical data to urge all patients with thromboangiitis obliterans to abstain from tobacco. However, for the large group of ambulatory patients with intermittent claudication from atherosclerosis the need for such restriction is not so clear. There is no evidence that tobacco, any more than mildly cold weather, adversely affects the course of the disease. Some investigators have been unable to demonstrate any deleterious effects of tobacco on intermittent claudication due to atherosclerosis. Others have permitted patients to smoke a few cigarettes daily without apparent harm. Tobacco smoking in many of these individuals is a well entrenched habit. For them abstinence may be neither necessary from the organic point of view nor desirable for emotional reasons.

Although there are cogent nonvascular reasons for discouraging the use of cigarettes, we no longer insist that patients with stable intermittent claudication secondary to atherosclerosis discontinue tobacco as part of the therapy of their peripheral arterial insufficiency.

III. *Assessing the Disability*

Having established the accuracy of the diagnosis and having satisfied oneself that all potentially related disorders have been adequately explored and treated, one comes to the third aspect of management: evaluation of the disability. At the outset, one must recognize and deal with the psychological hazards induced in the patient by the diagnosis itself. The significance of the disability to the patient is perhaps the most important limitation imposed by the syndrome. Failure to meet this problem squarely, particularly since a quick cure cannot be affected by drugs or surgery, will result in failure of treatment, loss of the patient or both. The fact that claudication will usually improve, or at least remain stationary and will not bar him from gainful employment should be clearly explained to the patient. This assurance will be reinforced when the patient observes that if he reduces his speed, he can walk further before experiencing pain. Many patients have developed a pattern of rapid walking and it may be necessary to reeducate them to walk more slowly. Finally, if the patient has a normal glucose tolerance test, one can use this finding to reassure him with regard to his fears concerning amputation.

IV. *Walking Program*

Almost routinely a walking program is recommended to each patient. The patient is urged to walk to pain tolerance at least four times daily. To present such therapy to a patient effectively, the physician must be convinced that the virtues of the plan are real. Walking to pain tolerance provides the most physiologic stimulus yet devised for the development of a collateral circulation in those areas where it is most needed, namely, the ischemic zone. Second, it offers the patient a specific program which is simple and completely safe. Gangrene of a toe cannot be induced by excessive walking, per se. Third, walking to pain tolerance has a most salutary effect on that large group of patients who, prior to seeing a physician, had voluntarily limited their activity to avoid pain. Invariably, these patients had assumed that the pain itself was in some way harmful or undesirable. Finally, the walking routine promptly acquaints the patient with improvement as it develops: a blood count or an oscillometric reading are not needed to convince him or to suggest to him that he is better.

V. *Foot Care*

In approximately half of the patients developing gangrene, a history is obtained of avoidable trauma, unnecessary minor surgery of the toes or the injudicious use of various local applications. Experience with ischemic extremities has repeatedly demonstrated that patients with extensive occlusive disease may be protected from gangrene by diligent care of

the feet. Conversely, in the presence of proved minimal occlusive disease a severe neglected insult to the leg may result in extensive gangrene even in the presence of pedal pulsations. It is this knowledge which fully justifies the effort involved in acquainting each patient with the minutiae of good foot care. This is particularly important among patients with diabetic neuropathy or impaired vision.

The following type of instructions may be profitably given to each patient with intermittent claudication.

(a) *Avoid Temperature Extremes.* Do not expose the feet to cold water or low temperatures that may produce frostbite. Do not bathe feet in hot water and avoid exposure of the legs to hot water bottles, electric pads, sun or ultraviolet light. The complaint of cold feet at night can frequently be relieved with warm socks and blankets rather than by the direct application of heat.

(b) *Avoid Mechanical Trauma.* Toenails must be trimmed carefully to avoid nicking the skin and cut straight across to prevent ingrowth of the nail. Rough nail edges or nail splitting can be avoided by soaking the toes in warm (not hot) water prior to cutting. If vision is poor or for any other reason difficulty is encountered in cutting the nails, they should be trimmed by a member of the family or a qualified chiropodist. Patients are advised that it is extravagant to save money on shoes. Shoes must fit well, be made of relatively soft leather, and be broken in slowly to avoid blisters. Coarse socks are undesirable because they tend to wrinkle. Corns and callouses can usually be traced to inadequate shoes or poor metatarsal arches. If these defects are corrected the thickened layers of skin will gradually soften and can be gently removed. If chiropody is necessary, the chiropodist should be informed of the vascular problem. The patient is instructed never to go about the house without slippers or walk barefoot at a beach, lest injury be incurred from some unsuspected object on the ground. Crowded places where the feet may be injured also demand special care on the part of the patient.

(c) *Local Hygiene.* The feet must be kept clean by frequent bathing (at least every other day). The skin must be thoroughly dried with a towel after bathing and then powdered with plain, nonmedicated talc. If feet perspire freely a change of socks preceded by powdering of the feet should be carried out twice daily. In addition to cleanliness and dryness, it is imperative that the skin be kept soft and pliable so that it remains free of cracks which can lead to gangrene. The application of a very thin layer of lanolin to the feet nightly is very effective in this regard. The feet may be covered with cotton or wool socks to avoid soiling the bed sheets. Excess lanolin should always be removed with cotton before applying the sock. Prevention of fungus infection can be achieved by keeping the feet dry and avoiding sources of contamination such as public baths, showers and swimming pools. Finally, no medicine or chemical should be applied to the foot unless prescribed by a physician.

In general, bland powders, lanolin, and certain nonsensitizing antibiotic ointments (for the treatment of local infections on advice of a physician) are the only substances that may need to be applied to the skin of the ischemic extremity.

(d) *Injury.* Minor injuries, particularly those involving a break in the skin, justify a call to a physician. When in doubt, bed rest and exposure of the foot to room temperature without the weight of bed clothes is the safest treatment until the doctor arrives.

Gangrene rarely appears *de novo* even in the limb with extensive old arterial obstruction. It usually develops because of the additional burdens produced by fresh arterial occlusion, diabetes, congestive heart failure, anemia, trauma and infection. At the present time, diagnostic and therapeutic measures are readily available to meet these major threats to the viability of the ischemic limb.

Case Reports

Case 1. Fresh Femoral Artery Occlusion, Producing Intermittent Claudication, Treated Effectively with Anticoagulants. Gradual Spontaneous Decrease in Claudication During Subsequent Twelve Months

J. L., a 46 year old stock room clerk, was hospitalized because of the recent onset of disabling leg

ain. Five days before entry, while walking down a orridor, the patient noticed a sudden, severe, dull che in the right calf which disappeared with cessaion of walking. Until admission, symptoms of achng, numbness and tingling persisted in the right leg. ifteen to 20 steps at his normal rate of speed preipitated the pain in the right calf. Pressure of the ole of the right foot against the car accelerator roduced numbness of the foot and calf.

Angina pectoris, dramatically improved by radioctive iodine (I^{131}) therapy, had been present for six ears. There was knowledge of allergy to various oods and drugs manifested by urticaria but no hisory of hypertension, myocardial infarction or iabetes.

Significant findings on examination were restricted to the lower extremities. The right foot was cooler to palpation than the left to a level of six inches above the malleoli. Only the femoral pulse was palpable on the right; all pulses were palpable in the left lower extremity. There was also, in the right leg, definite calf tenderness and a positive Homans' sign but no edema.

Urinalysis, blood count, electrocardiogram, chest x-ray and a glucose tolerance test were all within normal limits.

The patient was put to bed and received intravenous heparin every six hours for nine days. At this time, he developed urticaria immediately following each of two intravenous doses of heparin and the drug was discontinued. During the first week the temperature demarcation receded from a level six inches above the malleoli down to the toes. The patient was ambulated without further anticoagulant therapy and gradually permitted to increase his activity. Following the first day of heparin therapy calf tenderness and the positive Homans' sign disappeared.

Prior to discharge from the hospital a walking program was outlined for the patient and he was instructed concerning foot care. During the 12 months following discharge the patient's walking limitation from his claudication, though still present, had receded to a point where it no longer interfered with his work. None of the absent pulses returned.

Comment. In this patient the deposition of a fresh femoral artery occlusion manifested itself as intermittent claudication. In view of the cardiac history and the excellent pulses in the contralateral extremity, it is likely that the occlusion was embolic in origin. Immediate anticoagulant therapy was instituted to prevent the growth of the arterial clot, to retard the deposition of thrombi on atheromatous plaques distal to the fresh occlusion and finally to prevent the development of a pulmonary embolus secondary to the venous thrombosis which was obviously present in the patient's right leg on entry. The rather dramatic and progressive improvement in the claudication simply reflects the growth of an effective collateral circulation within several months unaided by any special therapeutic procedure other than repeated walking to the limit of pain tolerance. This case is typical of the spontaneous improvement in walking tolerance that continues to occur for many months after the onset of claudication. If this patient had had a sympathectomy, an embolectomy or a segmental arterial resection, the favorable result might readily have been credited to the surgical intervention.

Case 2. Intermittent Claudication, Two Years. Marked Improvement with Walking Exercises. Patient Never Stopped Smoking

F. S., a 42 year old businessman, came for advice because a sympathectomy had been recommended for the treatment of his intermittent claudication. Four months earlier, the patient noted the onset of tingling of the toes of the right foot while running for a train. Tingling and numbness in the toes of the right foot recurred whenever he ran but subsided promptly when the activity was stopped. One month later, on walking to work, the patient noticed that at the completion of a quarter mile distance he would develop a numbness in the right foot. The paresthesia was relieved by cessation of walking without sitting down: it never occurred while sitting or reclining.

Because of these symptoms the patient consulted an orthopedist who placed pads in the patient's shoes. This resulted only in a shift in the paresthesias from the toes to the longitudinal arch of the foot.

Examination of the feet revealed that only the dorsalis pedis pulsation was absent on the left. On the right the femoral and popliteal pulsations were full and bounding, the posterior tibial pulsation was present but markedly diminished and the dorsalis pedis pulsation was absent. Oscillometric readings were: left forearm, 6 units; left calf, 2 units, right calf, ½ unit. There was no true pallor on elevation or delayed rubor on dependency. Hair was present on the lower leg; there was no edema or nutritional change except that the skin over the dorsum of the right foot was dry and thickened.

Urine, blood count, electrocardiogram and a glucose tolerance test were all normal.

Because of considerable anxiety the prognosis and significance of intermittent claudication was carefully explained to the patient. The patient was instructed in foot care and in walking exercises. The nightly use of lanolin promptly softened the kera-

totic areas on the right foot. The patient who used one pack of cigarettes daily, was permitted to continue smoking. During the next 18 months, despite no change in the arterial pulsations or oscillometric readings, there had been a more than fourfold increase in the patient's walking tolerance.

Comment. This patient showed marked improvement in his claudication within an 18 month period despite continuance of cigarette smoking and with no therapy other than walking exercises. This case again illustrates the spontaneous improvement usually continuing for many months after the onset of claudication. The oscillometric findings added no information not already available from palpation of the pulses. The mechanical alterations in posture produced by foot pads were of interest in that they changed the muscles which developed the greatest ischemia so that the patient's symptoms were shifted from one area of his foot to another.

The extent of the arterial obstruction and the degree of the disability from claudication in this patient were very mild. The major problem was not the physical limitation per se but rather the fear of amputation and the concern over spread of the occlusive process to other vital areas. Permission to smoke, insistence on walking to tolerance, discussion of the significance of the normal glucose tolerance test, the negative electrocardiogram and the normal fundoscopic findings when coupled with improved walking tolerance without benefit of sympathectomy all contributed toward giving this patient considerable reassurance.

Case 3. Intermittent Claudication Five Years. Nocturnal Paresthesias Four Years, Incapacitating for One Month. Paresthesias Completely Relieved by Pyribenzamine With Return to Gainful Employment. No Change in Intermittent Claudication. Striking Therapeutic Result For Seventeen Months

J. B., a 50 year old chauffeur, was referred for advice concerning the use of sympatholytic agents in the treatment of his arterial insufficiency. Five years previously, the patient first noted pain in the right calf after walking five city blocks. The pain was relieved after five minutes by cessation of walking without sitting down. Beginning four years previously, the patient found that he was frequently awakened from sleep by a "burning" or a "pins-and-needles" sensation in his feet. He tried unsuccessfully to relieve these paresthesias by a number of maneuvers, including placing the leg in hot water. The paresthesias were diminished only by hanging the foot over the side of the bed. These sensory disturbances, which had been interpreted as reflecting advanced arterial insufficiency, had become so severe and frequent during the four weeks prior to referral that the patient was fatigued, irritable from lack of sleep and unable to work.

The patient had smoked 30 cigarettes daily for years. There was no history of diabetes or hypertension.

The significant findings on physical examination were restricted to the lower extremities. No pulses were palpable in either leg below the femoral triangle. The oscillometric reading at the right calf was zero and at the left calf was ¼ unit. There was marked pallor on elevation bilaterally; on dependency, rubor was delayed 25 seconds in the right leg compared with 15 seconds in the left extremity (normal less than 10 seconds) and the right foot was of a deeper hue than the left after two minutes of dependency. There was no hair below the knees bilaterally, but skin nutrition was otherwise good. In addition, varicose veins, slight ankle edema and pruritic scaly lesions between the toes were present in the right lower extremity.

Laboratory studies, including a urinalysis, blood count and a glucose tolerance test, were all within normal limits.

The disability from claudication was explained, a walking program outlined, and the patient instructed in proper foot care, including the avoidance of hot water. Potassium permanganate soaks were prescribed for the trichophytosis and quinine was given for the nocturnal paresthesias. The pruritic interdigital lesions disappeared with therapy. When no improvement resulted from the quinine, Pyribenzamine, 50 mg. at bedtime, was substituted with prompt relief of the paresthesias to the point where sleep was no longer interrupted. Temporary cessation of Pyribenzamine resulted in recurrence of paresthesias. This patient has now been followed for 17 months. He has continued uninterruptedly at work and is free of paresthesias at night. He still has claudication on walking 5 to 10 blocks, depending on his rate of speed but no longer finds this a significant disability.

Comment. In this patient with severe arterial insufficiency, nocturnal paresthesias, rather than claudication, was the limiting disability. Relief of the night pains by Pyribenzamine restored this patient to gainful employment.

No change in claudication was observed over a 17-month period during which time the patient abstained completely from tobacco. This case is typical of the lack of improvement in exercise tolerance after claudication has been present for several years. The patient did learn, however, that he could control the onset of claudication by his speed of walking. It was important in this instance to realize that the paresthesias did not represent an ischemic neuritis for which, at present, there is no satisfactory treatment. No further therapy for the intermittent claudication is contemplated. There is certainly no indication for the use of sympatholytic agents. Elastic stockings were not prescribed for the venous insufficiency because of the presence of advanced arterial occlusive disease.

Case 4. Intermittent Claudication Four Years. Infection in Weight Bearing Area of Congenitally Clubbed Foot. Amputation Avoided by Conservative Measures. Previously Unsuspected Diabetes Mellitus Recognized by Glucose Tolerance Test

M. G., a 70 year old shoe repairman, was referred for a possible amputation of the left leg. The patient had had crampy pain in the right calf on walking 5 to 10 blocks for four years. He had a left congenital clubfoot for which he had never received treatment. The extremity had been essentially asymptomatic until two weeks previously when a painful swelling followed by a small ulcer developed over the weight bearing inferior aspect of the left foot. Because of the vascular disease, the severe deformity of the foot and the presence of infection a supracondylar amputation had been recommended to the patient.

On two occasions in the past two years the patient had been hospitalized for episodes of acute myocardial infarction. During these illnesses both femoral and popliteal pulsations were readily palpable but the pedal pulses in both legs were absent. There had been no evidence of congestive failure, arrhythmia, anemia or glycosuria. A fasting blood sugar had been normal. Claudication had become more severe since the second myocardial infarction one year ago.

Examination revealed a left club foot. The femoral artery pulsations were palpable bilaterally. The popliteal and pedal pulses were absent. A painful tender swelling surrounding a small superficial ulcer was present over the lateral aspect of the cuboid bone. There was minimal surrounding cellulitis. The infection was treated locally with bacitracin ointment and bed rest. Subsequently, crutches were used to eliminate weight bearing on the left foot. The ulcer healed gradually over a four-week period. After several days of a high carbohydrate diet, a modified glucose tolerance test revealed that the venous blood sugars (Folin-Wu) one hour and two and one-half hours after the ingestion of 100 Gm. of glucose were 235 and 200 mg. per 100 cc., respectively. On the basis of this finding a diagnosis of diabetes mellitus was made. The patient was carefully instructed as to his diet and proper foot care. A special shoe was obtained and adjusted to prevent weight bearing on the lateral aspect of the foot. Subsequently, the patient was given walking exercises and during the past 12 months has been ambulatory and free of any difficulty with the left leg. The patient has adhered to his diabetic diet and the blood sugar levels have returned to normal values. Claudication in the right foot has remained unchanged.

Comment. Many factors favoring a decision to amputate were present in this patient: advanced age, two myocardial infarcts, absence of pulses below the femoral triangle, marked deformity of the foot, infection and diabetes. The infection, however, had been precipitated by a specific type of trauma which it was believed could be remedied by the use of a special shoe. The notorious risks of prolonged bed rest were avoided—once the lesion responded to antibiotics—by ambulation with the aid of crutches. Progression of the peripheral arterial insufficiency since the second myocardial infarct was manifested by loss of the popliteal pulsation, by aggravation of the claudication and by the inability of the skin to withstand an amount of trauma previously tolerated. Yet collateral circulation was adequate to permit healing of the ulcer when infection was controlled and trauma removed. The claudication in the contralateral extremity was not a disabling factor. The glucose tolerance test permitted the recognition and treatment of previously unrecognized diabetes mellitus. This case emphasizes that a negative urinalysis and a normal fasting blood sugar do not rule out a diagnosis of diabetes. Although this patient was saved from a major amputation, many threats to the viability of the extremities remain. Constant attention to the small details of good foot care will always be necessary.

SUMMARY

The diagnosis and therapy of intermittent claudication are critically reviewed. A detailed, concrete and positive program is described whereby every physician can effectively treat patients with intermittent claudication without recourse to intricate diagnostic or therapeutic techniques. The value of this program is illustrated with four case reports.

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ABSTRACTS

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AVITAMINOSIS

Wilgram, G. F., Hartroft, W. S., and Best, C. H.: Dietary Choline and the Maintenance of the Cardiovascular System in Rats. Brit. M. J. **2**: 1, (July 3), 1954.

Young male rats fed diets low in choline developed myocardial changes consisting of the appearance of fat droplets within the cells and areas of frank necrosis. The cardiac effects were aggravated by administration of a diet of high fat content. The extent of changes in the heart was by no means always parallel to that in the kidney.

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BACTERIAL ENDOCARDITIS

Beattie, J. W.: Enterococcal Endocarditis. Brit. M. J. **2**: 25, (July 3), 1954.

Of two cases of *Strep. fecalis* endocarditis reported, one patient, 63 years old, had had suprapubic prostatectomy with perineal urethrostomy eight months before the diagnosis of bacterial endocarditis was established and the other, 25 years old, had had a forceps delivery two months before. Both patients died, the first having received no treatment and the second chloramphenicol, penicillin and aureomycin. In the second patient treatment was seemingly relatively brief; yet the vegetations were said to be sterile at autopsy. The second case only had definite evidence of rheumatism by history and autopsy.

MCKUSICK

BLOOD COAGULATION

Lasner, S., and Volk, B. W.: Prolongation of Serum Prothrombin Time After Heparin. Proc. Soc. Exper. Biol. & Med. **86**: 428, (July), 1954.

Prothrombin consumption tests were performed on 20 individuals before and one hour after the intravenous administration of heparin. It was found that the prothrombin consumption time of serum of freshly coagulated blood was increased some seven fold when the test was done one hour after coagulation, and after heparin (50 mgm IV) increased some 10 fold when the test was done one hour after coagulation. Likewise, there was a seven fold increase in the interaction time of calcium, serum, and plasma one hour after heparin administration (50 mgm IV). The prolongation of these values is assumed to be due to the antithromboplastin activity of heparin.

HARVEY

CONGENITAL ANOMALIES

Mounsey, P. & Brigden, W.: The Apical Systolic Murmur in Mitral Stenosis. Brit. Heart J. **16**: 255, (July), 1954.

The operative findings were used to assess the significance of an apical systolic murmur in fifty individuals with clinical mitral stenosis.

A pan-systolic murmur is always associated with mitral regurgitation. Mitral regurgitation was not found in the absence of a systolic murmur. A murmur during the first half of systole is associated at most with slight regurgitation.

SOLOFF

Campbell, M.: Simple Pulmonary Stenosis: Pulmonary Valvular Stenosis with a Closed Ventricular Septum. Brit. Heart J. **16**: 273, (July), 1954.

Campbell describes in detail the characteristics of simple pulmonary stenosis as found in forty-four acyanotic and thirty-one cyanotic individuals. This syndrome is found in ten per cent of all cases of congenital heart disease.

Cyanosis is due to an inter-atrial septal defect or more rarely an unsealed foramen ovale. It is accompanied by polycythemia and clubbing of fingers and toes.

The syndrome is characterized clinically by a systolic pulmonary murmur with P_2 normal or diminished. Radiologically, the pulmonary artery is prominent and may pulsate. The right ventricle is prominent. The size of the cardiac silhouette varies from normal to considerable enlargement. In severer cases, a giant "a" wave is present in the jugular pulse. The electrocardiogram is always abnormal in the cyanotic group and frequently in the acyanotic. It is characterized by a large P wave in lead II and right ventricular preponderance with negative T waves in the right precordial leads. The right ventricular and atrial pressures are increased. The cardiac output may be normal. A left to right shunt was found in eighteen individuals due to the following defects: 1) anomalous pulmonary venous drainage 2) ventricular septal defects 3) patent ductus arteriosus and 4) mixed anomalies.

Campbell believes that operation is indicated if one of the following are present: 1) right ventricular pressure above 100 mm Hg 2) electrocardiographic evidence of right ventricular strain 3) giant "a" wave in the jugular pulse 4) severe symptoms or 5) enlargement of the heart.

SOLOFF

Lange, J. and Mundt, E.: The Sepsis Lenta in Congenital Malformation of the Heart. Ztschr. f. Kreislaufforsch. **43:** 448 (July), 1954.

A comparison of clinical data of 60 cases of subacute bacterial endocarditis in congenital heart disease (excluding coarctation of the aorta) with 70 cases of other etiology revealed the following differences in the course and symptomatology. In congenital malformation the sepsis starts at an earlier age (average 21) and takes a more rapid course. This may lead to difficulties in the differentiation from acute rheumatic fever complicating congenital heart disease. Unlike ordinary cases of subacute bacterial endocarditis there is no difference in the incidence in males and females with congenital heart disease. Which valves are affected depends on the character of the lesion. Pulmonary emboli, which are rare in the ordinary case with predominant left ventricular affections, are common when endocarditis develops on top of a congenital anomaly.

PICK

Wells, B.: The Assessment of Mitral Stenosis by Phonocardiography. Brit. Heart J. **16:** 261, (July), 1954.

The interval between the onset of QRS and that of maximal vibration of the first heart sound ("Q-1") and the interval between the beginning of the second heart sound and the beginning of the opening snap ("2-O.S.") were studied by logarithmic phonocardiography in thirty individuals with mitral stenosis. Three without an opening snap were discarded.

A short Q-1 means little stenosis and a short 2-O.S. means tight stenosis (verified by operation). The correlation is greater if both are used and corrected for a cycle length of 0.8 sec. If the first corrected interval minus the second corrected interval is over -1, severe mitral stenosis is present.

SOLOFF

CORONARY ARTERY DISEASE

Feldman, M. and Feldman, M., Jr.: The Association of Coronary Occlusion and Infarction in Diabetes Mellitus. A Necropsy Study. Am. J. M. Sc. **228:** 53 (July), 1954.

Diabetes mellitus is associated with a high frequency of cardiovascular disease which is related to the greater prevalence of atherosclerosis and coronary artery disease in these patients when compared with the non-diabetic population. In a study of 1319 consecutive adult necropsies, the authors found an incidence of 10.4 per cent of diabetes mellitus. Of the 137 cases of diabetes, there were 60 with associated coronary occlusion and infarction. The incidence of coronary heart disease in diabetics (43.8 per cent) was compared with 20.1 per cent incidence found in nondiabetic adults at necropsy. Thus coronary occlusion is twice as prevalent in the diabetic as in the nondiabetic. The coronary lesions occurred predominantly in the 6th and 7th decades; however, it was apparent that the onset of coronary heart disease had its onset at a younger age. There was a decided preponderance in females in the diabetic group (60 per cent) in contrast to the predominance of males among patients with coronary disease but without diabetes.

SHUMAN

Arons, J. J., and O'Rourke, P.: Myocardial Infarction with Aneurysm of Interventricular Septum and Perforation. J.A.M.A. **155:** 1050 (July 17), 1954.

A 68 year old man who had an acute posterior myocardial infarction developed an acute Bernheims syndrome with the sudden onset of a loud (Grade IV) systolic murmur maximal just to the left of the sternum at the 4th interspace. The diagnosis of septal perforation was then added. The patient survived 2 months but went downhill with dyspnea, cough, anorexia, weakness, cyanosis and progressive failure in spite of all treatment. Autopsy confirmed the clinical diagnosis.

KITCHELL

Bengtsson, E. and Örndahl, G.: Complications of Mumps with Special Reference to the Incidence of Myocarditis. Acta med. Scandinav. **149:** 381–388, (July 24), 1954.

The incidence of important complications was determined in 564 cases of mumps admitted to the Stockholm Hospital for Infectious Diseases. Meningoencephalitis occurred in one-half the cases, orchitis developed in one-half of the males and electrocardiographic changes suggesting myocarditis were recorded in 4.4 per cent of all patients. Myocarditis occurred in 6.6 per cent of the adults and 2.8 per cent of the children. Electrocardiographic changes were 5 or 6 times as common in girls as in boys. Of the 25 patients with electrocardiographic changes, 9 had relative tachycardia and 8 had transient soft murmurs. One patient showed transient cardiac enlargement and hypotension. Several patients complained of fatigue, precordial pain or tachycardia during convalescence. The electrocardiographic changes consisted of depression of the S-T segments, flattened, isoelectric or negative T waves, atrioventricular block (2 patients) or extrasystoles arising from multiple foci (1 patient). Slightly more than one-third of the patients with transient electrocardiographic changes showed concurrent elevation of the antistreptolysin titre.

ROSENBAUM

Karri, H.: Sudden Death Due to Myocarditis. A Clinical and Pathological Study. Acta med. Scandinav. **149:** 243–525, (July 15), 1954.

A series of eight cases is reported in which sudden death was attributed to chronic isolated myocarditis. In seven cases the pathological process was limited to the myocardium whereas in a single case there were pericardial adhesions in addition. The muscle fibres disclosed a chronic process with degeneration of the muscle fibers and moderate or extensive formation of fibrous tissue replacing the atrophied or destroyed muscle fibers. The primary changes in the myocardial fiber appeared degenerative rather than inflammatory. In a single case there was only a slight increase of the interstitial connective tissue without any collections of infiltrative cells. Neither hypertrophy nor atrophy of the fibers was present in this case. The involvement was localized primarily to the left ventricle. It was not possible to determine the exact duration in most cases but in each instance the microscopical picture suggested a persistent process. Three cases gave a history of tonsillitis prior to the sudden death.

ROSENBAUM

ELECTROCARDIOGRAPHY

Thomas, P. and Dejong, D.: The P Wave in the Electrocardiogram in the Diagnosis of Heart Disease. Brit. Heart J. **16:** 241, (July), 1954.

The authors record in detail the measurements and contours of the P waves in the standard and CR leads in health and in cardiac disease to determine if disturbances in the electrical activity of the right atrium can be distinguished from that of the left. CR leads are used because they give larger auricular complexes.

One hundred normals, seventy-one with mitral valve disease, ten in addition with generalized cardiac enlargement, sixty-one with hypertension, thirty-nine with pulmonary disease, fifty with congenital heart disease and thirteen with constrictive pericarditis were studied.

Four major deformities of the P waves were found 1) bifid a) with first peak more prominent b) with equal peaks c) second peak more prominent d) and less common blunted peaks 2) diphasic (+−) 3) pointed 4) convex.

The normal P wave is never more than 3.0 mm. high (average 1.3 mm.), 0.10 sec. in duration (average 0.063 sec.) and when bifid, more than 0.04 sec. between peaks.

Increasing abnormalities of the P wave occurred with increasing severity of mitral stenosis. These abnormalities are characterized by 1) increased number of second peaked P waves in left precordial leads 2) increase in average peak interval 3) increase in amplitude.

The P wave was normal in the hypertensive group without failure. Two of twelve with failure showed a second peak type of P in CR_7 and one was of an equal peak type.

Emphysema without failure manifested few significant findings. Those with failure and cases with primary pulmonary hypertension showed significant changes characterized by a P of normal duration but increased height. The P waves were pointed almost equally in all leads.

In pulmonary stenosis, there was likewise an increase in the number of tall and pointed P waves. The peak interval was increased in atrial septal defect. The P wave was normal in patent ductus arteriosus and abnormal in only one of fifteen with ventricular septal defect.

The P wave was abnormal in constrictive pericarditis with increased number of bifid waves with increased peak interval.

The first peaked type of P was found in leads CR_1–CR_4 and the second peaked type in CR_4–CR_7. A prolonged peak interval was found in abnormal records of cases showing abnormality of the left atrium. The tallest waves were found in pulmonary stenosis and moderate to severe mitral stenosis.

The authors conclude that right atrial abnormality is present if P in lead CR_1 is above 2.5 mm. and is diphasic, pointed or bifid of the first peak type. Left atrial abnormality is present if the peak interval is prolonged or if P in CR_4–CR_7 is bifid of the second peak type and taller than 3.0 mm. If both characteristics are present, there is combined atrial abnormality.

SOLOFF

Gross, A.: Genesis and Interpretation of the Electrocardiogram. Anesthesiology **15:** 378, (July), 1954.

The author discusses the fundamentals of electrocardiography by means of the question and answer method as well as by diagrams. The factors of depolarization and repolarization producing the major deflections of the electrocardiographic tracing are enumerated and the bipolar and unipolar leads are explained with their normal values. Axis deviation and cardiac position are illustrated. The findings of myocardial strain, myocardial infarction and heart block are discussed and a logical approach to the diagnosis of arrhythmias is described.

SAGALL

Selinger, A. G., and Levin, S. L.; Use of Ballistocardiography in Evaluation of Paroxysmal Rapid Heart Action, J.A.M.A. **155:** 897 (July 3), 1954.

The occurrence of paroxysmal rapid heart action calls for an evaluation of the cardiovascular status of the patient. Such rapid heart action is fundamentally a functional disturbance but may occur in either structurally normal or abnormal hearts. The authors suggest that when history, physical examination, x-ray studies, and electrocardiogram are all within normal ranges, an abnormal ballistocardiogram may be very significant. This is especially true if such a ballistocardiogram is grossly abnormal (Brown, Grade 3 or 4).

KITCHELL

Ippolito, T. L., Blier, J. S. and Fox, T. T.: Massive T-Wave Inversion. Am. Heart J. **48:** 88, (July), 1954.

Massive T-wave inversion is an infrequent electrocardiographic finding. Three case reports were presented of patients who each had this electrocardiographic abnormality. An analysis of these cases in addition to others reviewed from the literature suggests that two factors are essential in the genesis of massive T-wave inversion: (1) a very slow ventricular rate, such as may occur during complete heart block; and (2) a coronary insult, either in the form of a myocardial infarction or coronary insufficiency. If these two factors are etiologically related, then perhaps the following sequence may explain massive T-wave inversion: the repolarization of a locally damaged heart may be delayed if the intraventricular volume is increased (prolonged diastole) and intraventricular pressure built up.

MAXWELL

Berman, R., Simonson E., and Heron, W.: Electrocardiographic Effects Associated With Hypnotic Suggestion in Normal and Coronary Sclerotic Individuals. J. Appl. Physiol., **7:** 89, (July), 1954.

Hypnotically induced states of anxiety-fear and work pain (angina pectoris) were studied on 14 normal young people and 11 patients with varying degrees of coronary artery disease and angina pectoris. Twelve lead electrocardiograms were recorded before and during the hypnotic state.

In the normal group either type of suggestion produced T wave changes (elevation in 2 and depression in 5) in 7 cases or 50 per cent. All cases had an increased pulse rate. In the group with coronary artery disease, 4 cases or 36 per cent showed T wave changes (inversion in 3 and elevation in 1) and 1 case had loss of an R wave in lead III. The T wave changes are compatible with coronary insufficiency.

These results indicate that nervous factors may aggravate angina though they have not been proven to cause angina. Since electrocardiographic changes can be produced by nervous factors, the emotional state should be considered in interpreting electrocardiograms.

WECHSLER

Wells, B.: Phonocardiography. Brit. M. J. **2:** 9, (July 3), 1954.

The phonocardiogram may assist with the following features of the first heart sound: delay of the first sound in mitral stenosis, differentiation of crescendic first sound from a true presystolic, the identification of a first sound in the presence of loud murmurs. It may contribute the following information about the second sound: physiological splitting due to asynchronous closure of the arterial valves, better transmission of the aortic component to the apex and elucidation of the opening mitral snap of mitral stenosis. By measurement of duration the PCG permits differentiation of a short diastolic murmur from a long third heart sound which is rarely more than 0.16 seconds in duration. The origin of systolic murmurs can be identified, in part at least. Ejection-stenosis murmurs are diamond-shaped. That of aortic stenosis ends before the second sound; that of pulmonic stenosis reaches the aortic but not the delayed pulmonic component of the second sound. The murmurs of mitral and tricuspid regurgitation and ventricular septal defect fill all of systole. Tricuspid murmurs tend to show much variation with respiration. In patent ductus arteriosus the intensity of the murmur is maximal around the second sound and minimal around the first sound; this feature permits differentiation from to-and-fro aortic or pulmonic murmurs or the identification of separate but coexisting murmurs. Like the EKG the phonocardiogram has contributed to our knowledge of the heart and at the same time is becoming less essential as that knowledge is obtained.

MCKUSICK

ENDOCRINE EFFECTS ON CIRCULATION

Dörner, J.: Comparative Investigation on the Circulatory Effects of Adrenalin and Arterenol in

the Animal Experiment. Arch. f. Kreislaufforsch. **21:** 88, (July), 1954.

The authors compared in 50 dogs the effects of intravenous and intra-arterial injection of L-adrenalin and L-arterenol (0.01–1.0 γ/kg) upon blood pressure and blood flow through various vascular areas. The data were based on about 800 different determinations using Rein's thermostromuhr for measurements of blood flow.

Blood supply to the hind legs was found increased after intravenous injection of the two drugs, but more so by arterenol. This occurred in the intact extremity as well as following removal of the skin. A similar effect of the two was observed upon the coronary blood flow. Reduction of blood flow was found in the common and internal carotid arteries and in the intestinal and renal vessels. This action was more pronounced with adrenalin than with arterenol. The latter, however, showed more pronounced pressure effect than the former. The heart rate responded to both to an equal extent.

On the basis of these data the authors conclude that there is no principal qualitative difference in the action of adrenalin and arterenol upon the peripheral vessels and upon blood pressure. No evidence was found that the observed blood pressure elevation was due to increased cardiac output following adrenalin injection, and was caused by a peripheral vasoconstriction following arterenol. Since pressure effects of the two drugs in the unanaesthetized animal paralleled those found in man, there is no reason to believe that in man two such different mechanisms may come into operation in increasing the blood pressure. The principal difference between the actions of the two drugs is the effect upon the heart rate. In the animal experiment both adrenalin and arterenol accelerate the heart, in man arterenol slows the heart beat.

PICK

HYPERTENSION

Livesay, W. R., Moyer, J. H., and Miller, S. I.: Treatment of Hypertension with Rauwolfia Serpentina Alone and Combined with Other Drugs. J.A.M.A. **155:** 1027 (July 17), 1954.

A total of 84 cases of hypertensive vascular disease, observed in clinics for 2 months to 3 years before treatment was started, are here reported. Forty-three patients were treated with alseroxylon alone, and 20 obtained significant reductions in blood pressure. Of 21 patients treated with alseroxylon plus hydralazine, 12 (or 57 per cent) showed responsiveness; 8 of these were cases who failed to respond to alseroxylon alone. Of 39 patients treated with alseroxylon plus hexamethonium, 36 (or 92 per cent) were responsive. Rauwolfia serpentina derivatives are valuable when used alone in milder hypertension. Fewer side effects and better control in patients with severe hypertension was noted when rauwolfia was used in combination with hydralazine and hexamethonium.

KITCHELL

Byrom, F. B.: The Pathogenesis of Hypertensive Encephalopathy and Its Relation to the Malignant Phase of Hypertension. Experimental Evidence from the Hypertensive Rat. Lancet **2:** 201, (July 31), 1954.

The author presents evidence to support the view that hypertensive disease is of two main grades of severity each with its own basic physiology. In the first, vasoconstriction is diffuse and distribution of blood to the tissues remains substantially normal except where it is locally impeded by degenerative arterial changes. In the second, focal but widespread pathological spasm is superimposed on the diffuse vasoconstriction with resulting (1) transient disturbances of function or (2) increased capillary permeability with attendant focal edema or (3) local necrosis of the arterial wall and/or the tissue supplied. In the rat the arterial spasm which underlay the various changes could be abolished by lowering of blood pressure but not consistently by cervical sympathectomy.

MCKUSICK

PATHOLOGIC PHYSIOLOGY

Isaacs, J. P., Berglund, E. and Sarnoff, S. J.: Ventricular Function. III. The Pathologic Physiology of Acute Cardiac Tamponade Studied by Means of Ventricular Function Curves. Am. Heart J. **48:** 66 (July), 1954.

Acute cardiac tamponade was studied in dogs by means of ventricular function curves, the continuous recording of systemic blood flow, and pressures in the right and left atria, the pulmonary artery, the aorta, and the pericardium. In other experiments pressures were measured in the inferior vena cava and right atrium, and in the pulmonary veins and left atrium. The effect of increasing blood volume during various degrees of tamponade was also observed.

A measurable pressure gradient was not found between the vena cava and right atrium or between the pulmonary veins and left atrium either in the control or tamponade state. The hemodynamic consequence of acute cardiac tamponade, therefore, cannot be explained on the basis of inflow obstruction at the entrance of the veins into the pericardium.

Ventricular function curves were suppressed during cardiac tamponade. This was not due to functional impairment of the myocardium, which conformed with Starling's law of the heart during tamponade as well as during the control state. Rather, the weakness of cardiac contraction was directly attributable to the reduced effective filling pressure in diastole, the latter being due to the

restraining influence of the elevated pericardial pressure.

An increase of blood volume produced a significant increase of aortic pressure and cardiac output in mild to moderate tamponade but produced little improvement of these values in severe tamponade. In all degrees of tamponade, infusions elevated both right and left atrial pressures and these were at much higher levels when tamponade was severe.

These observations demonstrate that the circulatory defect in tamponade is brought about by a limitation of the pericardial space available for the diastolic expansion of the ventricles. The consequent shortening of diastolic ventricular fiber length results in less ventricular work. The aortic pressure and cardiac output thus decline even while atrial pressures are markedly elevated.

Some clinical and therapeutic implications of these findings were discussed.

MAXWELL

Bashour, F. and Winchell, P.: Stokes-Adams Attacks and Cushing's Syndrome. New England J. Med. **251**: 105–107, (July 15), 1954.

A patient, aged 36 years with features of Cushing's syndrome is described in detail. Symptoms of Cushing's syndrome first appeared at age 17. Treatment included irradiation to the pituitary fossa. At age 33 the patient began to have episodes of fainting. The patient had several Stokes-Adams attacks during a 24-hour interval in the hospital. These were treated with oxygen inhalation and ephedrine, 25 mg. every two hours. The electrocardiogram changed from complete heart block to 2:1 atrioventricular block, left bundle-branch block and 1st-degree heart block. The patient was discharged on a program of ephedrine, 125 mg. daily and had no episodes of syncope for 14 months thereafter. Since arteriosclerosis is said to be frequent in Cushing's syndrome, it is assumed to be the basic etiology of the Stokes-Adams attacks observed in this woman.

ROSENBAUM

Daly, M. De B., Lambertson, C. J., and Schweitzer, A.: Observations on the Volume of Blood Flow and Oxygen Utilization of the Carotid Body in the Cat. J. Physiol., **125**: 67, (July), 1954.

It is possible that the changes in carotid chemoreceptor responses accompanying a drop in blood pressure may be due to a decrease in blood flow through the carotid body with changes in O_2 and CO_2 tensions and consequent stimulation. Therefore, carotid body blood flows and arteriovenous O_2 differences were measured in anaesthetized cats. All but one of the veins from the region of the carotid body were ligated and this one was cannulated. A graduated glass tube was attached to the cannula and the time of the advancing blood column measured.

The normal blood flow was 38 cu. mm per minute (range 22 to 55) at a mean arterial blood pressure of 130 mm Hg (range 105 to 150). Hypotension was induced by bleeding and the blood flow dropped with it. Intravenous adrenaline increased the mean arterial blood pressure and blood flow. Occlusion of the common carotid artery decreased the carotid body blood flow. There was no detectable arteriovenous O_2 difference with normal carotid body blood flow. However, when the blood flow fell to 9 cu. mm per minute, an arteriovenous O_2 difference of 2 volumes per cent was found.

These results indicate that you can get stimulation of the carotid body receptors by intrinsic anoxemia with a normal arterial O_2 tension. In addition, the carotid body has a greater blood flow in proportion to its weight than any other tissue (2,000 ml per 100 gm of carotid body per minute).

WECHSLER

Whitney, R. J.: Circulatory Changes in the Forearm and Hand of Man with Repeated Exposure to Heat. J. Physiol., **125**: 1, (July), 1954.

The mercury-in-rubber strain gauge was used to record changes in the volume of the forearm. The advantage of this method over the plethysmograph is that the arm was not enclosed in an artificial environment. An appendix on this method is presented. The method was applied with and without arterial occlusion at the wrist to differentiate forearm and hand blood flow. Other measurements included rectal and skin temperatures, metabolic rates, changes in forearm venous reservoir, distensibility of forearm venous reservoir and sweat loss. Four healthy young males were studied. Twenty minute work periods were alternated with twenty minute rest periods. Temperature was 45.6 C dry bulb and 29.1 C wet bulb.

There was much variation in response. The only consistent change was a decrease in the forearm volume. The extent and rapidity of the change showed that it was probably caused by a change in the size of the venous reservoir or venoconstriction, which may be an important compensatory mechanism. Arterial occlusion at the wrist caused a decrease in forearm volume.

WECHSLER

Platts, M. M. and Whitaker, W.: The Diagnostic Importance of the Blood Carbon Dioxide Content of Patients with Central Cyanosis. Am. Heart J. **48**: 77, (July), 1954.

The arterial blood carbon dioxide contents were measured in 55 patients with central cyanosis (congenital heart disease or chronic bronchitis and emphysema, with and without complicating congestive heart failure). The values were below normal (44–52 vol per cent) in the majority of patients with cyanotic congenital heart disease, normal or increased in the majority of patients cyanosed from chronic bronchitis and emphysema, and invariably

i reased in patients with congestive heart failure, c mplicating chronic bronchitis and emphysema.

The results indicate that the arterial carbon d xide content is of diagnostic importance in p tients with central cyanosis. A value less than t e lower limit of 44 vol per cent suggests congenital h art disease, whereas one above the upper normal l mit of 52 vol per cent favors chronic pulmonary d sease as the cause of central cyanosis in a patient w ose diagnosis is uncertain from clinical examina- t n. These relationships are even more invariably t e in the presence of congestive heart failure, com- p icating congenital heart disease, or a chronic p lmonary disorder.

MAXWELL

Stephenson, H. E., Jr., Reid, L. C., and Hinton, J. W.: Pitfalls, Precautions, and Complications in Cardiac Resuscitation. Arch. Surg. **69:** 37, (July), 1954.

On the basis of a study of over 1,200 case reports of cardiac arrest from various portions of the world, the authors arrived at certain conclusions regarding the complications and pitfalls likely to be encountered in attempting to treat this condition.

The first step in the therapeutic approach is the early diagnosis of the condition. Only 6 per cent of the patients will survive a delay of over 4 minutes from the time cardiac arrest occurs. An emergency cardiac team is not practicable, since such a group can not be assembled rapidly enough even under the most optimal conditions. Therefore, it behooves the surgeon and his assistants to become acquainted with the technic of quickly opening the chest and beginning cardiac massage. The latter should be performed in a manner that results in adequate oxygenation of the cerebral cortex, and it should be continued as long as irreversible damage to the brain has not taken place. One complication which may result from too active massage is rupture of the myocardium, a possibility which is minimized if the heart is compressed with the pericardium intact. Intra-arterial transfusion is preferred if replacement of blood loss is required. At all times there should be available some type of resuscitator for the maintenance of active oxygenation of the blood and an electric defibrillation to counteract ventricular fibrillation.

ABRAMSON

Brofman, B. L., and Perez-Alvarez, J. J.: Successful Treatment of Cardiac Arrest. Arch. Surg. **64:** 12, (July), 1954.

The authors point out that for massage to be successful in the treatment of cardiac arrest, there must not be any structural interference with the movement of blood through the heart, and a normal blood volume must be present. Therefore, if mitral stenosis exists, it is necessary to minimize the obstruction as quickly as possible by surgical means. Furthermore, severe blood loss should be counteracted by rapid reinfusion of blood. If there is traction or rotation of the heart so as to occlude large vessels, the organ must immediately be replaced in its normal anatomical position. Restoration of the heart beat is also aided by the judicious use of such drugs as epinephrine, procaine amide, atropine, calcium gluconate and lanatoside C.

ABRAMSON

Lee, G. de J., Matthews, M. B. & Sharpey-Schafer, E. P.: The Effect of the Valsalva Maneuver on the Systemic and Pulmonary Arterial Pressure in Man. Brit. Heart J. **16:** 311, (July), 1954.

The Valsalva maneuver was used to compare the vasomotor responses of the systemic and pulmonary arterial systems simultaneously in ten individuals. Bradycardia was prevented by atropine.

The Valsalva maneuver was followed by a rise in systemic pressure and also in right atrial, pulmonary and capillary pressures. These latter rises are interpreted as due to a rapid increase in right ventricular filling pressure. Tetraethyl ammonium chloride in three individuals abolished the systemic pressure rise but not that of the pulmonary artery.

SOLOFF

Boe, J. and Benestad, A. N.: Reticulocyte Reaction Following Cerebral Ischemia. Investigations of the Reticulocytes before and after Induced Syncope, in a Patient with Postural Hypotension, Acta med. Scandinav. **149:** 345–348, (July 24), 1954.

Observations were made of the reticulocyte levels in the blood of a patient with postural hypotension during a control period of several days and before and after hypotension and syncope induced by the erect position. Postural hypotension was found to induce a distinct reticulocyte reaction with the predominant increase occurring in the more immature forms. This reaction was attributed by the authors to variations in the cerebral oxygen tension due to the induced cerebral ischemia. The observations made are felt to support the hypothesis of Seip that the oxygen tension in the erythropoietic center in the basal part of the brain, is an essential factor in the liberation of reticulocytes into the peripheral blood.

ROSENBAUM

Hegnauer, A. H. and D'Amato, Henry E.: Oxygen Consumption and Cardiac Output in the Hypothermic Dog. Am. J. Physiol. **178:** 138 (July), 1954.

Dogs were exposed to immersion hypothermia. During the early period of shivering cardiac output and oxygen use were increased. Later both these parameters decreased steadily until at 17°C the oxygen use was 15 per cent and output 10 per cent of control values. At this same temperature, work

output is 7 to 8 per cent of normal. Oxygenation of the heart is adequate until the heart stops in a systole or fibrillation. The arterio-venous oxygen difference increases during increased oxygen use or static hypoxia. It returns to normal after the oxygen debt is paid.

OPPENHEIMER

Beikert, A.: Development and Evaluation of Working Hypertrophy of the Heart, the Adrenals, and Hypophysis. Studies in Animal Experiments. Arch. f. Kreislaufforsch **2:** 115, (July), 1954.

Conditions of training were reproduced in guinea pigs by forcing the animals to swim over daily increasing periods of time, with gradual reduction of rest periods in between. After a training period of 4 months the maximal efficiency was tested by letting the animal swim until complete exhaustion. Then the results were compared with a corresponding experiment in a control group of untrained animals.

The comparison revealed that the working capacity in the trained group greatly exceeded that of the untrained group and post-mortem studies revealed a significant increase in the weight of the heart, the hypophysis and the adrenals in the former. However, animals with most marked organ hypertrophy proved less efficient than those in which hypertrophy of the heart and hypophysis was less pronounced. No such inverse relationship was found between the size of the adrenals and the working capacity. Furthermore, hypertrophy of the heart was invariably associated with enlargement of the hypophysis but not with enlargement of the adrenals.

On the basis of these experiments it is concluded that the functional state of the hypophysis has a profound influence on the development of cardiac hypertrophy. It would appear that the less economic the work of an individual, and the worse its adaptation to increased work load, the greater the strain during each training period and the more marked the hypertrophy of both hypophysis and heart subsequent to the stress. The parallelism in the development of hypertrophy in two organs suggests a mutual and causal interrelationship of the two processes.

PICK

PHARMACOLOGY

Jacobson, E., and Adelman, M. H.: The electrocardiographic effects of intravenous administration of Neostigmine and Atropine during cyclopropane anesthesia. Anesthesiology **15:** 407 (July), 1954.

Continuous electrocardiograms were obtained in twenty patients under cyclopropane anesthesia before, during, and after the intravenous administration of neostigmine. At the height of the electrocardiographic evidence of neostigmine activity, atropine sulfate (0.8 mg) was administered intravenously. In all patients neostigmine induced some electrocardiographic change. These occurred individually or in combinations and consisted of disruption of auriculoventricular conduction, sinus depression, sinus arrest, increased amplitude of QRS and increased prominence of the T wave. These are interpreted as classical cholinergic effects of varying intensity. Atropine given intravenously produced opposite effects (adrenergic activity) manifested by cardiac irritability, multifocal ventricular extrasystoles and ventricular flutter. No difference of the neostigmine effects was noted in curarized or non-curarized patients.

In discussing these results the authors find no evidence to support the contention that atropine potentiates the cholinergic action of neostigmine on the heart by central vagal stimulation, since these electrocardiographic findings after atropine were adrenergic. These studies also suggest that sudden death after intravenous neostigmine and atropine in anesthetized patients may be attributed to either (1) the cardio-inhibitory action of neostigmine or (2) the adrenergic effect of neostigmine and atropine with resulting ventricular fibrillation.

SAGALL

Lee, K. S.: Effect of Quinidine on Papillary Muscle. Proc. Soc. Exper. Biol. & Med. **86:** 444, (July), 1954.

Using a technique whereby simultaneously, oxygen consumption of cat's papillary muscle and strength of contraction can be measured, the effect of quinidine was studied. It was found that addition of a solution of quinidine (1:10,000 conc.) caused a decrease in the strength of contraction but only a very slight decrease in oxygen consumption. Anaerobic glycolysis, also, was not affected by quinidine in this concentration.

HARVEY

Pereva, G. A.: Rauwolfia Serpentina in Hypertensive Vascular Disease. Proc. Soc. Exper. Biol. & Med. **86:** 453, (July), 1954.

Observations upon the effects produced by Raudixin (50–100 mgm b.i.d.) given orally to ten uncomplicated ambulatory hypertensives, to ten hospitalized patients with hypertension who had in addition some degree of nitrogen retention, retinopathy with oedema, and proteinuria, and to four other hypertensives on the metabolic ward, are described. Careful studies of the blood pressure, pulse, urinary function, and blood chemical composition were made. Some reduction in the resting blood pressures of seven of the ten ambulatory patients was effected during the period of drug administration, but the reduction was not great. No effect was noted on those patients with more ad-

nced changes associated with the hypertension on the hemodynamics or the renal function.

HARVEY

Rosenman, R. H., Freed, C. S. and Friedman, M.: Effect of Desoxycorticosterone Acetate upon the Blood Pressure of Rats Fed Varied Dietary Intakes of Potassium and Sodium. J. Clin. Endocrin. & Metab. **14**: 661 (June), 1954.

Five groups of rats, in which hypertension failed to develop consequent to uninephrectomy and the application of a unilateral renal ligature, were injected with DCA and concomitantly fed diets varying in their content of sodium and potassium. The results indicated that an adequate intake of potassium is essential for the development and persistence of DCA-induced hypertension but that excess potassium intake does not potentiate the pressor effect of DCA. It further was found that DCA induced a depressor response when the dietary sodium/potassium ratio was increased. Apparently the action of the potassium supplement in permitting DCA hypertension to develop is one of replacing the loss of this cation induced by DCA and thus preventing the potassium depletion which would otherwise block its potential pressor effect.

MAXWELL

Lindsay, A. E. and Brown, H.: Clinical Experience With P-Sulfonamido-Benzoic Acid, a Carbonic Anhydrase Inhibitor, as a Diuretic Agent. J. Lab. and Clin. Med. **43**: 839 (June), 1954.

Dirnate (p-sulfonamido-benzoic acid), a powerful carbonic anhydrase inhibitor, was given to eight hospitalized patients to screen its usefulness as a diuretic agent. Studies were carried out on a Metabolic Ward and were well controlled. The oral route was employed in nine patients, dosage being 2 gms. every six hours. Four patients were given the drug intravenously in the dosage of 20 mgm. per Kg body weight in 250 ml. of 5 per cent dextrose solution. On the oral dosages sodium and potassium excretion was not increased; weight loss did not occur. Serum electrolyte levels, blood gas levels, and whole blood pH did not change. In one patient given the drug intravenously, urine flow increased eight fold, sodium excretion six fold, and potassium excretion four fold, but the effects were only of several hours duration. In four patients comparison of response to Dirnate and Thiomerin were made. In two the response was nil for each drug; in two others the response to Thiomerin was prompt diuresis and nil to Dirnate. Toxicity to Dirnate was slight. One patient had nausea and vomiting when the drug was given orally. Tingling in fingers was reported by patients given the drug intravenously.

HARVEY

Herbst, F. S. M. and Hurley, N. A.: Effects of Heparin on Alimentary Hyperlipemia. An Electrophoretic Study. J. Clin. Investigation **33**: 907 (June), 1954.

Normal individuals were given a fatty meal and electrophoretic patterns of the serum were studied before and after the intravenous injection of heparin. Electrophoretic analysis was made by paper electrophoresis as well as moving boundary electrophoresis. The results indicate that the lipid band, normally present in the beta globulin area, was then in the area of alpha-2 or alpha-1 globulin. Furthermore, the lipid band normally present in alpha-1 globulin area now migrated ahead of albumin. Other electrophoretic determinations showed a decrease in the beta-1 globulins and an increase in the alpha-2 or alpha-1 globulins. These electrophoretic changes are probably not specific for heparin. Storage of both fasting and hyperlipemic sera in a refrigerator at 5°C. for three to four weeks gave patterns similar to those after heparin.

WAIFE

Bernstein, S. H., Feldman, H. A., Harper, O. F. and Klingensmith, W. H.: Mass Oral Penicillin Prophylaxis in Control of Streptococcal Disease. Arch. Int. Med. **93**: 894 (June), 1954.

Oral administration of 250,000 units of penicillin twice daily for 10 days successfully aborted a Group A Streptococcus disease epidemic and markedly reduced the carrier rate for at least five to six weeks. Few penicillin reactions were observed with this schedule. The reactions were predominately urticarial, with a few serum-sickness-like illnesses. There was no evidence that the orally administered penicillin produced significant amounts of diarrhea.

BERNSTEIN

VanderKolk, K., Dontas, A. S. and Hoobler, S. W.: Renal and Hypotensive Effects of Acute and Chronic Oral Treatment with 1-Hydrazinophthalazine (Apresoline) in Hypertension. Am. Heart J. **48**: 95 (July), 1954.

The effect of acute and chronic oral administration of Hydralazine on the resting renal circulations and the basal blood pressures of 7 patients with moderate essential hypertension was studied by means of renal clearances (p-aminohippurate and inulin).

Well-tolerated oral doses of Hydralazine produced definite renal vasodilatation associated with a moderate decrease in blood pressure and increase in heart rate, these effects lasting about 4 hours. Prolonged treatment (11–15 weeks), however, diminished these responses considerably. In only 3 of 7 patients examined after two months or more of chronic treatment was there a slight but definite increase in resting renal plasma flow. No change in the basal blood pressure was noted in any of the patients studied. Observations of foot flow (venous occlusion plethysmography) in these patients dem-

onstrated that the extremital circulation shared in the vasodilator response to Hydralazine.

MAXWELL

Bernstein, L. M., Pascale, L. R., Schoolman, H. M. and Foley, E. F.: Intravenous Procaine Amide as an Aid to Differentiate Auricular Flutter with Bundle Branch Block from Paroxysmal Ventricular Tachycardia. Am. Heart J. **48:** 82, (July), 1954.

Five cases of auricular flutter with bundle branch block which simulated paroxysmal ventricular tachycardia were presented. In each case the correct diagnosis was established by the electrocardiographic changes following intravenously administered procaine amide. These changes included: (1) transient decrease of atrioventricular conduction from 2:1 to 4:1; (2) decreased atrioventricular conduction revealing flutter waves in the increased SQ segments; (3) a slightly irregular ventricular rhythm with second degree atrioventricular block changing to a more rapid regular rhythm as auricular slowing and 1:1 atrioventricular conduction occurred; and (4) change in F-R intervals so that F waves which had been obscured became discernible between QRS complexes.

Since digitalis preparations may be hazardous in the treatment of ventricular tachycardias, it is suggested that any paroxysmal tachycardia with prolonged QRS complexes be considered as ventricular in origin and treated in that manner until a supraventricular origin can be conclusively demonstrated.

MAXWELL

Pascale, L. R., Bernstein, L. M., Schoolman, H. M. and Foley, E. F.: Intravenous Procaine Amide in the Treatment of Cardiac Arrhythmias. Am. Heart J. **48:** 110, (July), 1954.

Intravenous procaine amide was used in the treatment of 33 patients with 40 episodes of paroxysmal tachycardia; this included paroxysmal ventricular tachycardia, paroxysmal supraventricular tachycardia (auricular or nodal) and auricular flutter. The results were correlated with previous reports from the literature in an attempt to evaluate in which types of arrhythmia procaine amide is effective.

Procaine amide was effective in well over 50 per cent of the patients with supraventricular tachycardias, its effect being limited at times by the occurrence of episodes of hypotension. By contrast, however, this drug was completely ineffective in the treatment of auricular flutter, and in fact sometimes caused serious and deleterious increases in the ventricular rate. It was felt, therefore, that procaine amide has no place in the treatment of auricular flutter. All instances of ventricular tachycardia were converted by intravenous procaine amide. Much larger doses than the usually recommended 1000 mg. were sometimes necessary to terminate the tachycardia; when hypotension occurred, l-norepinephrine was given intravenously in addition to the procaine amide.

In this series, the toxicity of intravenously administered procaine amide included hypotension, convulsions, and widening of the QRS complexes. Hypotension was related to the rate of administration and total dose, and was controlled when necessary by the constant infusion of l-norepinephrine. General widening of the QRS complex was not considered a contraindication to continuing therapy; on the other hand, therapy was terminated if a normal QRS was altered to a bundle branch block type of QRS.

MAXWELL

Akers, R. P., Hershey, S. G., and Zweifach, B. W.: Blood-Borne Vasoactive Substances Produced by Splanchnic Nerve Stimulation. Am. J. Physiol. **178:** 63, (July), 1954.

When the distal end of the greater splanchnic nerve is stimulated, a vasoexcitor material, previously undescribed, appears in the blood of rats. This material is detected by increased vascular reactivity in the terminal mesenteric bed to epinephrine. This same material, detected by bioassay in blood of stimulated rats, could reproduce in test animals the results seen in mesenteries of stimulated ones. Spleen, kidneys and adrenals could be removed without changing the response. The adrenal cortex was concerned in chronic experiments. The "epinephrine potentiating" principle was mediated by sympathetics.

OPPENHEIMER

Beher, W. T. and Anthony, W. L.: Effect of Dihydrocholesterol and Soy Bean Sterols on Elevated Tissue Cholesterol. Proc. Soc. Exper. Biol. & Med. **86:** 589, (July), 1954.

Mice with a high liver cholesterol content, fed a diet high in dihydrocholesterol, did not show an increased rate of mobilization of liver cholesterol, nor did the high serum cholesterol levels in rabbits fall when the rabbits were fed soy bean sterols.

HARVEY

Spies, S. W.: Effect of a Mercurial Diuretic on Thyroid Uptake and Renal Clearance of Radioiodine. Proc. Soc. Exper. Biol. & Med. **86:** 469, (July), 1954.

A study of eight patients was undertaken to determine the effect the administration of a mercurial diuretic had upon the radioactive iodine uptake of the thyroid and the excretion of this halogen by the kidney. Well controlled studies were done upon the uptake by the gland on the eight as well as renal clearance of the radioactive material on four of these patients. It was found that there was no effect upon radioactive iodine uptake on the thyroid, nor on the renal clearance of this material following the intramuscular injection of meralluride sodium. There was

marked increase in the chloride excretion, however, following the injection.

HARVEY

aylor, R. C., Minor, J. B., and Friedberg, C. K.: Influence of Carbonic Anhydrase Inhibitors on Renal Effects of Acute Respiratory Alkalosis and Acidosis in Human Subjects. J. Appl. Physiol., **7**: 43, (July), 1954.

In 8 normal hospitalized patients respiratory kalosis or acidosis was induced by 30 minutes of yperventilation or 15 to 30 minutes of inhalation 5 to 20% CO_2. Five of these subjects took 750 mg. Diamox before the experiments. Specimens of urine were collected anaerobically every 15 minutes and analyzed for pH, Na, K and HCO_3. Venous blood pH and CO_2 were done. Glomerular filtration rates were measured by the inulin or endogenous creatinine clearance rates.

Respiratory alkalosis diminished the renal reabsorption of HCO_3 and K. Diamox potentiated this effect. Respiratory acidosis increased the renal reabsorption of HCO_3 and K. Diamox impeded this increase. Reabsorption of HCO_3 was not related to plasma HCO_3 levels. The urine pH rose during respiratory alkalosis and fell during respiratory acidosis. There was no significant change in Na excretion.

These results suggest that plasma pCO_2 levels influence renal HCO_3 reabsorption.

WECHSLER

PHYSICAL SIGNS

Tourniaire, A., Blum, J., Deyrieux, F. and Tartalier, M.: Premonitory Syndrome of Chronic Cor Pulmonale. Arch. d. mal. du coeur **47**: 591, (July), 1954.

Based on the study of 49 own observations with chronic pulmonary disease or kyphoscliosis the authors describe the symptomatology of a syndrome considered to represent a "prodromal stage" of chronic cor pulmonale which can be recognized on clinical grounds without hemodynamic studies.

The presenting symptom frequently is chest pain. Right ventricular hypertrophy is evident from pulsations in the epigastric area and can be confirmed at x-ray examination by bulging of the middle left salient in the A-P view, narrowing of the retrosternal space in the left transverse diameter, and pulsatile dilatation of the branches of the pulmonary arteries. The electrocardiograms show, however, only a displacement of the heart but no right heart strain. Catheterization reveals systolic pulmonary hypertension of the "precapillary" type, and systolic pressure elevation in the right ventricle. The diastolic pressure is normal unless heart failure sets in. There is usually a moderate peripheral O_2 desaturation, increasing on exercise.

The main points of a successful therapeutic approach to such cases consist in rest, prophylaxis of broncho-pulmonary infection and use of bronchodilators, particularly aminophyllin, all of which prevent development of right heart failure and tend to reduce the pulmonary hypertension.

PICK

Eddleman, E. E. Jr., Willis, K., Walker, P. P., Christianson, L. and Pierce, J. R.: Relationship of the Physiologic Third Heart Sound to the Jugular-Venous Pulse. Am. J. Med. **17**: 15 (July), 1954.

The physiologic third heart sound was found in eleven of sixty young, normal subjects. The phonocardiographically recorded sound occurred at the peak of the "V" wave in the jugular-venous pulse, suggesting that the physiologic third heart sound is the result of the opening of the atrioventricular valves and is in reality a "physiologic opening snap".

HARRIS

PHYSIOLOGY

Marks, R. M., Shedd, C. G. and Locke, A. W.: Volvulus of the Gall Bladder Associated with Acute Myocardial Infarction. Report of a Case and Review of the Literature. New England J. Med. **251**: 95-97, (July 15), 1954.

A woman, aged 79 years, who was admitted to the hospital six hours after the onset of symptoms, is described. The initial impression was acute cholecystitis and probable angina pectoris due to hypertensive arteriosclerotic heart disease. On the second day in the hospital, the physical signs pointed to an abnormality in the right upper abdomen and a laparotomy was performed. This disclosed a volvulus of the gall-bladder with infarct necrosis of the gall-bladder and chronic cholecystitis. The patient died on the fifth day in the hospital and post-mortem examination disclosed a massive infarction of the left anterior myocardial wall, an abnormality which had been suggested strongly by electrocardiograms taken shortly after the onset of symptoms and prior to the surgical procedure.

ROSENBAUM

Brecher, G. A. and Hubay, C. A.: A New Method for Direct Recording of Cardiac Output. Proc. Soc. Exper. Biol. & Med. **86**: 464, (July), 1954.

A method for measuring cardiac output is presented. A device which consists of a bristle flowmeter within a cannula which can be inserted into the pulmonary artery or into the aorta is described in detail. With this device, direct measurements were made of the pulmonary artery pressure and flow in dogs.

HARVEY

Meroney, W. H. and Herndon, R. F.: The Management of Acute Renal Insufficiency. J.A.M.A., **155**: 877 (July 3), 1954.

In a study of acute renal insufficiency in war casualties, it was found that total fluid intake per 24 hours should vary between 500 to 800 cc. plus the measured output. Potassium intoxication, the only chemical abnormality that threatens the patient's life during the first week of oliguria, produces no clinical signs or symptoms until death is imminent. The electrocardiogram is a rather accurate gauge of plasma potassium levels if there is no other abnormality except hyperpotassemia. Plasma calcium is depressed, however, when potassium is elevated, because of the associated retention of inorganic phosphate. As calcium is a specific antagonist of potassium, its administration causes striking modification of the electrocardiographic effects of potassium intoxication. Digitalis has a similar and additive effect to calcium, so caution must be exercised if the two are used together. Administration of sodium or dextrose with insulin lowers the plasma potassium level. Continuous infusion of a standard mixture of calcium, sodium, and dextrose will protect the patient from potassium intoxication for days. If clinical uremia occurs, artificial kidney dialysis is indicated. Six hours of dialysis may restore electrolyte balance and relieve symptoms. Dialysis should be repeated each time symptoms recur until renal function is recovered. Anemia should be treated with small transfusions of 200 to 300 cc. Purpuric hemorrhage is not a contraindication to dialysis in these patients. After diuresis is established, the kidneys may excrete salts wantonly, so sodium chloride and potassium chloride may have to be added to the regular diet for about a week.

KITCHELL

RHEUMATIC FEVER

Szabo, M. A.: Abdominal Pain in Rheumatic Fever. Bull. St. Francis Sanatorium **10**: 42 (Apr.), 1954.

A case of abdominal manifestations of rheumatic fever simulating acute appendicitis is presented to bring into focus the difficulty encountered in differential diagnosis. It is pointed out that abdominal pain, although a frequent clinical manifestation of rheumatic activity, has not been stressed in the literature with sufficient emphasis. The diagnostic criteria of acute suppurative appendicitis and pseudoappendicitis of rheumatic origin may be indistinguishable. Pseudoappendicitis occurs almost invariably at the onset of a rheumatic attack and the abdominal signs may be the first manifestation of rheumatic fever. The abdominal pain may be diffuse in the beginning but frequently becomes localized in the right lower quadrant. The pain diminishes and tends to disappear in the course of two to six days and as this occurs, joint pains may appear. In other instances the abdominal and joint pains set in at approximately the same time, suggesting the diagnosis of rheumatic fever.

All of these criteria may yet fail to differentiate the two conditions. It is suggested that a test dose of salicylates be given in such cases before the patient is subjected to surgery.

BERNSTEIN

Latscha, B. I., D'Allaines, F. and Lenegre, J.: The Pressure in the Left Atrium and Ventricle Before and Following Commissurotomy. Arch. d. mal. du coeur **47**: 385 (May), 1954.

In 70 patients submitted to mitral surgery, the pressure in the left atrium and left ventricle was determined by direct puncture of the respective chamber in the opened chest, before and after the performance of commissurotomy.

Left atrial pressure which is markedly elevated in all types of severe mitral stenosis is considerably lowered by a successful commissurotomy. The average reduction of maximal pressure was from 31.7 to 16.3 mm. Hg, and of the minimal pressure from 17.4 to 7.85 mm. Hg. In pure and predominant mitral regurgitation, the atrial pressure may be subnormal. Left ventricular systolic pressure was found low in all varieties of mitral stenosis, particularly so in its pure form (average 78.4 mm Hg), and rising after satisfactory splitting of the valve to an average value of 115 mm Hg. It is often elevated in the presence of mitral regurgitation. The diastolic left ventricular pressure is normal in mitral stenosis except when it is associated with aortic insufficiency.

Simultaneous recordings of left ventricular and aortic pressure revealed the surprising fact that in mitral stenosis the latter may be higher than the former. The difference may decrease or disappear following commissurotomy.

The ratio of right and left ventricular pressure in the studied material correlated well with anatomical data established by others referring to weight relation of two ventricles in mitral disease.

PICK

Heffer, E. T., Turin, R. D., Slater, S. R. and Kroop, I. G.: An Evaluation of Large Doses of Cortisone in First Attacks of Rheumatic Carditis. J. Pediat. **44**: 630 (June), 1954.

An uncontrolled study in 19 children between ages of 5 and 15 of treatment with large doses of cortisone (200–300 mgm. per day) in the initial attack of rheumatic carditis is presented. In each, the classic signs of rheumatic pancarditis were present. Treatment was carried on for two to three weeks, after which tapering of the dosage was done. Although all patients showed the effects of large dosages with development of a "Cushing" picture, there were no deleterious toxic effects. The initial anti-rheumatic effect was striking in all instances within three days of onset of therapy. Follow-up studies from six to 25 months have failed to show development of any valvular lesion. The authors conclude that large amounts of cortisone and cor-

tinued treatment for a "long enough period" may prevent residual cardiac damage.

HARVEY

Engelman, E. P., Hollister, L. E. and Kolb, F. O.: Sequelae of Rheumatic Fever in Men, J.A.M.A. **155:** 1134 (July 24), 1954.

Rheumatic fever in children is well documented but the literature contains few studies of the disease in adults. This report is based on a four to eight year follow-up study of 135 veterans who had been hospitalized for rheumatic fever during World War II. Rheumatic heart disease as a sequel to rheumatic fever in adults was found in 32 patients (23.7 per cent) of the 135. Only 18.4 per cent of 98 veterans who had had an initial attack of rheumatic fever during military service showed residual heart disease. This low incidence furnishes confirmatory evidence that prognosis is relatively more favorable when rheumatic fever first occurs during adult life. The cardiac status of these patients remained remarkably stable in the interval between acute illness and follow-up study. Ninety-five per cent were gainfully employed or in school at follow-up study and no instance of serious disability due to sequelae of rheumatic fever was observed.

KITCHELL

Thomas, G.: Heart Failure in Children with Acute Rheumatic Carditis. Brit. M. J. **1:** 205, (July 24), 1954.

Conflicting opinions as to the efficacy of digitalis in the heart of acute rheumatic fever may have been engendered in part by failure to distinguish cases of pericardial effusion from those of myocarditis. True primary myocardial failure is probably rarer than previously supposed. Effusion often occurs early in an attack; myocardial failure develops, as a rule, only after a prolonged period of rheumatic activity. There are usually well-marked murmurs by this time. In contradistinction to the findings with pericardial effusion, the temperature, sedimentation rate and leucocyte count are less likely to show striking elevation and the response to digitalis is satisfactory. Rapid changes in the size of the cardiovascular silhouette are characteristic of pericardial effusion.

McKUSICK

ROENTGENOLOGY

McKusick, V. A.: The Study of Mitral Regurgitation by Roentgen Kymography, with Observations on the Movements of Cardiac Calcifications. Am. J. Roentgenol. **71:** 961 (June), 1954.

The author presents illustrations of sites where left atrial pulsations may be studied by conventional roentgen kymography in patients with mitral valvular disease: (1) on the impression of the barium filled esophagus; (2) when the left atrium forms a part of the right or left contours, or posteriorly in the right anterior oblique position; (3) by motion of calcific deposits in the left atrial wall. The diagnosis of mitral insufficiency requires the demonstration of early systolic expansion, or motion in the same direction as in ventricular systole.

It is pointed out that factors other than mitral insufficiency might also produce outward movement of the atrial wall in systole, but, in general, the author feels that the correlation with other clinical evidence for mitral insufficiency is good enough to warrant the use of this method. The author also presents a method for estimation of the volume of blood regurgitated based on the maximal increment in outline in a somewhat overpenetrated roentgen exposure in the postero-anterior position, superimposed on the volume of the left atrial hemisphere.

SCHWEDEL

SURGERY

Black, H. and Harken, D. E.: Safe Conduct of the Patient Through Cardiac Surgery. With Special Reference to Diseases of the Mitral and Aortic Valves. New England J. Med. **251:** 45–51, (July 8), 1954; **251:** 85–91, (July 15), 1954.

The authors present a broad outline of recommendations for the management of patients undergoing cardiac surgery, particularly procedures upon the mitral and aortic valves. In the discussion of preoperative preparation it is mentioned that overdigitalization has been encountered more commonly than insufficient dosage of the drug. It is pointed out that potassium chloride is indicated in the treatment of digitalis toxicity but that supplemental potassium should be withheld on the day prior to operation so that the patient does not face the usual postoperative oliguria with an excess of potassium. It has been the custom of these workers to digitalize all patients who are to undergo a valvuloplasty even though normal sinus rhythm is present and the drug has not been required previously, because atrial fibrillation occurring postoperatively may be more rapidly controlled and the direct cardiotonic effect of the drug is believed to protect against congestive failure as the left ventricle becomes adjusted to the increased volume of blood it is called upon to pump. Quinidine and procaine amide or procaine hydrochloride are believed contraindicated as routine prophylactic measures because of their depressing effect upon the myocardium and the fact that such depressed hearts go into cardiac arrest more frequently. The demonstration of hyponatremia prior to operation is a particularly ominous sign but in most patients with this abnormality efforts to correct it by oral or intravenous infusion of saline have been futile. Routine administration of saline solution to all patients about to undergo cardiac surgery as a measure to prevent postoperative hyponatremia is considered unwise and, in some instances, dangerous.

Diuretics should be used to bring the patient down to his minimum or dry weight but the last preoperative dose should be given at least forty-eight hours before the operation. Patients with congestive heart failure are placed on a low-salt diet (200 mg. of sodium) unless hyponatremia is present and patients with hepatic enlargement are placed on a high-carbohydrate, low-fat diet with vitamin supplements. Patients who have been on long term anticoagulant therapy are taken off the drug and the prothrombin time allowed to return to normal before operation. Parenteral injection of penicillin is begun forty-eight hours before operation and in patients with chronic pulmonary suppuration complicating mitral stenosis, this is supplemented with aerosol penicillin and streptomycin. It is stated that in more than 700 cardiac operations upon patients with rheumatic heart disease, there have been only 3 overt cases of reactivation of rheumatic carditis in the immediate postoperative period and few subsequent significant attacks of acute rheumatic fever. It is also said that "dramatic improvement almost invariably follows the relief of significant mitral stenosis even in cases in which the evidence is very suggestive of active carditis". A significant number of patients with subacute bacterial endocarditis have apparently undergone successful valvulotomy within several weeks following control of the bacteremia.

The attitude of the attendants prior to operation is important in prevention of tachycardia, anxiety and apprehension. Anaesthesia consists of pentothal given intravenously followed by nitrous oxide, oxygen and ether with curare for intubation. Cyclopropane was discontinued when it was found to increase the tendency to cardiac irritability. The importance of adequate ventilation is stressed and the intravenous use of prostigmine in doses of 0.25 mg. to reduce tachycardia is mentioned. Norepinephrine or Nor-synephrine may be used to treat hypotension. Replacement of blood, minute-to-minute is recommended because it has been found that the enlarged heart of chronic rheumatic disease and severe mitral stenosis tolerates hemorrhage poorly. The intrapericardial injection of procaine to prevent cardiac irritability has been abandoned because of undesirable myocardial depression. Ventricular fibrillation is treated by intracardiac injection of procaine (10 cc. of 1% solution) or potassium chloride (10 mEq. in 10 cc.) to produce standstill followed by manual systole to restore beating and sometimes supplemented by calcium chloride (10 cc. of 10% solution) or epinephrine (1.0 mg. in 10 cc. of saline). Electrical defibrillation has been quite unsuccessful in the experience of these observers. Cardiac arrest is treated by washing out the anaesthetic agent with hyperventilation with 100 per cent oxygen and gentle intermittent cardiac compression; calcium chloride or epinephrine may be injected directly into the left ventricle. Embolization to the brain is prevented by passing rubber dam drains about the right innominate, left common carotid and left sub-clavian vessels and kinking these vessels for no more than one to one and one-half minutes during the dangerous portion of the intracardiac maneuver.

Recommended postoperative measures include use of the Fowler's position, oxygen administration, antibiotics, elastic stockings to reduce the likelihood of pulmonary emboli, encouragement of cough to clear retained secretions, and early ambulation. If rapid fibrillation should develop with apical rates inadequately controlled with the maintenance doses of digitalis, this program may be supplemented with Digoxin, Cedilanid or ouabain. All patients with mitral stenosis and normal sinus rhythm and all who have undergone a transventricular cardiotomy are given quinidine prophylactically postoperatively. It is said that prior to this practice, seventy-five per cent of patients undergoing valvuloplasty who were in normal rhythm fibrillated after the operation. If, in operations upon the mitral valve, heavily calcified or clumsy leaflets are encountered, heparin is given to prevent the formation of fresh clots and late embolization. A similar practice is followed after the correction of aortic stenosis. However, if cerebral emboli occur, heparin is withheld because of possible increase in cerebral damage by perivascular extravasation of blood. Low serum sodium levels occurring postoperatively may be due to a shift of sodium from serum into cells, dilution of serum or depletion of the body stores of sodium.

Fluid intake by all routes is restricted to 1500 cc. in the first 24 hours post-operatively. Specific indications for postoperative intravenous use of hypertonic saline solutions include (a) postoperative oliguria associated with hyperkalemia and serious cardiac irregularities; (b) hyponatremia persisting beyond four or five days in spite of a technically satisfactory corrective procedure and (c) progressive depression of the serum sodium concentration to 120 mEq. per L. or below within 48 hours after operation associated with disorientation, depression and hypotension. Quinidine prophylaxis is continued for six weeks to two months in all patients with normal rhythm prior to operation and for four to six months in those with transient fibrillation in the postoperative period. No definite opinion is expressed regarding attempts to revert chronic auricular fibrillation to normal after successful valvuloplasty.

ROSENBAUM

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ANNUAL MEETING AND SCIENTIFIC SESSIONS

A tentative schedule has been approved by the Program Committee of the Scientific Council for the Association's 28th Scientific Sessions to be held in conjunction with the Annual Meeting in New Orleans from October 22 through 26. The three-day scientific programs will include both general morning sessions, open to all, and specialized afternoon sessions designed for those specifically interested in one of the sections of the Scientific Council.

The Scientific Sessions will open on Saturday morning, October 22 and continue through the following Monday. Section dinners have been arranged for Saturday and Sunday evenings, and the Association's annual dinner will be held on Monday evening.

Also of interest to the medical profession will be the program of the Community Service and Education Council on Sunday, October 23, and the joint program to be conducted by the Council on Rheumatic Fever and Congenital Heart Disease and the Community Service and Education Council, Monday morning, October 24.

Films and Exhibits

Because this year's Annual Meeting and Scientific Sessions are being held independently of any other major medical meeting for the first time, the range of activities and features of interest to the medical profession has been considerably broadened. Plans include special exhibits and presentation of an extensive film program. There will be space for 28 such exhibits, including one being prepared by the Association's Medical Division.

Arrangements are also being made for a post-meeting medical tour to Mexico. Details of the tour will be published in later issues of CIRCULATION.

Abstracts

Those wishing to present papers at any of the scientific sessions are invited to submit abstracts in duplicate, not to exceed 300 words, before July 1. Send the abstracts to Medical Director, American Heart Association 44 East 23 Street, New York 10, N.Y. The tentative schedule for the scientific and community program sessions follows:

Scientific Sessions

Saturday, October 22: Morning—General session, Section on Cardiovascular Surgery and Section on Clinical Cardiology. *Afternoon*—Lewis A. Conner Memorial Lecture; general session, Section on Clinical Cardiology; specialized session, Section on Cardiovascular Surgery; specialized session, Section on Basic Science jointly with Section on Circulation. *Evening*—Dinner of the Section on Cardiovascular Surgery.

Sunday, October 23: Morning—General session, Section on Basic Science jointly with Section on Circulation and Section on Clinical Cardiology. *Afternoon*—General session, Section on Clinical Cardiology; specialized session, Section on Basic Science jointly with Section on Circulation. *Evening*—Dinners of the Section on Basic Science and the Section on Circulation.

Monday, October 24: Morning—General session, Council for High Blood Pressure Research and Section on Clinical Cardiology; papers on rheumatic fever. *Afternoon*—General session, Section on Clinical Cardiology; specialized session, Council for High Blood Pressure Research; papers on rheumatic fever.

Community Program Sessions

Sunday, October 23: First Annual Program—Council on Community Service and Education.

Monday, October 24: Morning—Joint program of the Council on Community Service and Education and the Council on Rheumatic

Fever and Congenital Heart Disease. *Afternoon*—Annual Business Meeting of Council on Community Service and Education; Annual Business Meeting of Council on Rheumatic Fever and Congenital Heart Disease.

SHOW AHA EDUCATION EXHIBIT TO MAJOR MEDICAL MEETINGS

An exhibit illustrating the services performed by Heart Associations for the medical profession has been prepared by the Professional Education Committee and is being viewed by an estimated 25,000 physicians at four major medical gatherings.

The exhibit, which shows aspects of the research, professional education and community service programs of the Association, was first seen at the Los Angeles meeting of the American Academy of General Practice in March. Subsequently it was shown in San Francisco at the April meeting of the Federation of American Societies for Experimental Biology and at the New Orleans gathering of the Southern Branch of the American Public Health Association this month.

Its next scheduled appearance will be at the American Medical Association meeting in Atlantic City, June 6–10.

AUDIO-VISUAL KIT FACILITATES HOME STUDY

"Cardiac Clinics" a newly devised audio-visual kit is now available to physicians through their Heart Association. Contained in the kit are a medical discussion, recorded on 33⅓ rpm long-playing discs, and accompanied by a script of the discussion, correlated 2″ x 2″ slides and a table-top viewer for the slides.

The kit is designed primarily for home or office use and is intended particularly for physicians who do not have educational facilities readily available. It can also be used in small meetings by adding projection and sound amplification equipment.

The initial kit in the series is "The Role of the PA Film of the Chest in Cardiology," prepared by Dr. William R. Christensen, Professor of Radiology, University of Utah College of Medicine. It is now available through the Association and its affiliates.

NEW "CARDIO-VIEWS" KITS UTILIZE 3-D PHOTOGRAPHY

The first of a new series of three-dimensional visual kits, designed for use in teaching and in individual study, is now being prepared by the Medical Division. The kits utilize stereoscopic photography and a simple viewer for 3-D slides. They will be known as "Cardio-Views."

The first in the series of kits will be ready shortly. It illustrates each of 12 heart models, presenting PA, RAO and LAO views with corresponding silhouettes imprinted above on 16mm. stereoscopic color film. There are 36 views in all.

RESEARCH GRANTS DEADLINE ADVANCED TO NOVEMBER 1

Applications for grants-in-aid for the fiscal year 1956–57 under the national-affiliate research support program must be submitted by November 1, 1955. This is a month earlier than in previous years. The change was made in order to allow for the greater volume of applications which must be reviewed by the Research Committee. The deadline for applications for fellowships remains at September 15.

MANUAL OUTLINES STANDARDS FOR CARDIOVASCULAR CLINICS

A new edition of "Recommended Standards for Cardiovascular Clinics" has been issued by the Association. It replaces a previous edition published in 1949. The clinics manual is designed to offer criteria for the guidance of clinics committees and other persons responsible for the establishment and maintenance of cardiovascular clinics.

Minimum requirements are set forth for medical, social, nursing and other ancillary services. It describes the Association's yardsticks for certification of clinics, noting that "certification of a clinic by an affiliated Heart Association implies that the clinic is giving the best service available in that community." Emphasis is placed on providing facilities which will enable patients to continue or return to productive life, rather than becoming physically and economically dependent.

Issuance of the clinics guide underlines the importance of clinic development in the community programs of many local Heart Associ-

ions. Copies of "Recommended Standards" may be obtained by physicians, clinic committees and other professionals concerned with the subject from local Heart Associations or from the American Heart Association, 44 East 23 Street, New York 10, N. Y.

NEW DIRECTORY OF RHEUMATIC FEVER CONVALESCENT FACILITIES

A revised edition of the "Directory of Facilities for care of Patients with Rheumatic Fever and Rheumatic Heart Disease" has been issued by the Helen Hay Whitney Foundation. The edition brings information on such facilities throughout the United States and its territories up to date. It is designed to be of particular interest to physicians who are faced with the problem of finding adequate convalescent facilities for rheumatic patients.

The directory includes such information as number of beds, number of beds set aside for rheumatic fever and rheumatic heart disease patients, sex and age requirements for admission, financial requirements and some of the practices employed in care of patients. The number of rheumatic fever and rheumatic heart disease admissions during the last fiscal year is also listed for each institution.

The revised edition is a project of the "Clearinghouse of Information" on rheumatic fever and rheumatic heart disease established by the Helen Hay Whitney Foundation with the cooperation of the American Heart Association. The "Clearinghouse" is now maintained by the Foundation. The "Clearinghouse" also has extensive bibliography files providing basic information on research in the rheumatic fever field, epidemiology, prophylaxis, diagnosis, treatment, recurrences, community programs, recreational facilities, etc.

Additional information on these activities and copies of the directory and bibliographies can be obtained from Miss Dora E. Young, Executive Secretary, The Helen Hay Whitney Foundation, 525 East 68th Street, New York 21, N. Y.

AHA JOINS IN PROGRAM AT RHEUMATISM MEETING

The annual joint program of the Association's Council on Rheumatic Fever and Congenital Heart Disease and the American Rheumatism Association will be presented at the Rheumatism Association's Annual Meeting in Atlantic City, June 4. The following presentations have been scheduled for inclusion in the program:

The Isolation and Characterization of the Non-Specific Hyaluronidase Inhibitor of Human Blood—Gerald S. Berenson, Joyce K. Newman, Martin B. Mathews and Albert Dorfman, Chicago.

Immunological Evidences of Group A Streptococcal Infections in Patients Undergoing Mitral Commissurotomy—W. F. Lynch, Gene H. Stollerman, M. A. Dolan, D. Young and J. B. Schwedel, New York.

A Study of Changes in Serum Concentrations of the Enzyme, Glutamic-Oxalacetic Transaminase, in Rheumatic Fever (Preliminary Report)—Irwin Nydick, James Tang, Gene H. Stollerman, Felix Wróblewski and John S. La Due, New York.

Relation of Incidence of Heart Damage in ACTH and Cortisone Treated Rheumatic Fever to Dosage and to Duration of Illness—Sujoy B. Roy and Benedict F. Massell, Boston.

The Effect of Large Doses of Cortisone in First Attacks of Rheumatic Carditis—Milton Markowitz and Ann G. Kuttner, Baltimore and New York.

MAY 31 ABSTRACT DEADLINE FOR ARTERIOSCLEROSIS PAPERS

The deadline for submission of abstracts for those who wish to present papers at the 1955 meeting of the American Society for the Study of Arteriosclerosis is May 31. The meeting is to be held at the Sheraton Hotel, Chicago, November 6 and 7. Factual abstracts (original and four copies) should be sent to Charles F. Wilkinson, Jr., M.D., Program Chairman, 550 First Avenue, New York 16, N.Y.

DR. ARTHUR S. CAIN APPOINTED AS ASSISTANT MEDICAL DIRECTOR

Arthur S. Cain, M.D. has joined the staff of the Association as an Assistant Medical Director. In announcing the appointment, Charles D. Marple, M.D., Medical Director, said that Dr. Cain will aid in the administra-

tion of the national research support program conducted by the Association and its affiliates in the field of cardiovascular diseases.

Dr. Cain is experienced as a medical teacher, research investigator, administrator and writer. He has been engaged in full-time research and teaching at the Department of Physiology of the Columbia University College of Physicians and Surgeons. Dr. Cain also served as Director of Surgery at the Kansas City Municipal Hospital and as a representative of the American College of Surgeons in the investigation of hospital standardization.

The new assistant medical director received his medical degree from the University of Kansas and interned at the Albany Hospital before being appointed as a teaching fellow at Dartmouth Medical School. He is a diplomate of the American Board of Surgery.

EUROPEAN CARDIOLOGY MEETINGS SET FOR 1956

Among important European cardiologic meetings announced for 1956 are:

The International Cardiologic Sessions in Lisbon, Portugal, January 24–29, sponsored by the Center of Cardiologic Studies of the Institute of Higher Learning of the Lisbon Faculty of Medicine.

The Second European Congress of Cardiology in Stockholm, September 1–14. Information on the Congress can be obtained from Dr. Karl Erik Grewin, Södersjukhuset, Stockholm, Sweden.

MEETINGS CALENDAR

May 23–27: National Tuberculosis Association, Milwaukee, Mrs. Morrell DeReign, 1790 Broadway, New York 19.

June 2: The Endocrine Society, Atlantic City, H. H. Turner, 1200 N. Walker Street, Oklahoma City.

June 3–4: American Rheumatism Association, Hotel Dennis, Atlantic City. W. H. Kammerer, 33 East 61st Street, New York 21.

June 4: North American Chapter of the International Society of Angiology, Hotel Chalfonte, Haddon Hall, Atlantic City. Henry Haimovici, M.D., 105 E. 90th Street, New York 28, N. Y.

June 5: Society for Vascular Surgery, Atlantic City, George D. Lilly, 25 S.E. Second Avenue, Miami 32, Fla.

June 6–10: American Medical Association Annual Meeting, Atlantic City. Dr. George F. Lull, 535 North Dearborn Street, Chicago 10.

June 13–17: New Gordon Research Conference on Blood, Kimball Union Academy, Meriden, New Hampshire. Herbert L. Davis, Ph.D., Department of Biochemistry, University of Nebraska College of Medicine, Omaha 5.

ABROAD

May 23–26: International Surgical Congress, Geneva, Switzerland. Dr. Max Thorek, 1516 Lake Shore Drive, Chicago.

May 26–31: Seventh International Congress of Comparative Pathology, Lausanne, Switzerland. Professor Hauduroy, 19 rue Cesar Roux, Lausanne.

May 29–June 3: International Hospital Congress, Lucerne, Switzerland. Capt. J. E. Stone, International Hospital Federation, 10 Old Jewry, London E.C. 2, England.

June 13–17: American Pediatric Society, Quebec City, P.Q. A. C. McGuiness, 237 Medical Laboratory, University of Pennsylvania, Philadelphia.

June 13–17: European Congress on Rheumatism, The Hague, Netherlands. Dr. H. van Swaay, Pieter Bothstraat 12, The Hague.

June 13–18: American Society for Pediatric Research, Québec City, P.Q. Sydney S. Gellis, 330 Brookline Avenue, Boston 15.

June 18–19: Fifth Congress of the International Association for the Study of the Bronchi, Stockholm, Sweden. Dr. Stahle, Kohlmarsanatoriet, Sweden.

June 20–22: Canadian and British Medical Associations, joint meeting, Toronto, Canada. Dr. Arthur D. Kelly, 244 St. George Street, Toronto.

June 21–25: Commonwealth Health and Tuberculosis Conference, Royal Festival Hall, London, England. Mr. J. H. Harley Williams, Tavistock House North, Tavistock Square, London W.C. 1.

July 4–8: Congress of the International Diabetes Federation, Cambridge, England. James G. L. Jackson, Diabetic Association, 152 Harley Street, London W.C. 1, England.

July 23–29: Sixteenth Congress of the International Society of Surgery, Copenhagen, Denmark. Dr. L. Dejardin, 141 rue Delliard, Brussels, Belgium.

July 25–30: International Anatomical Congress, Paris, France. Professor Gaston Cordier, 45 rue des Saints-Pères, Paris 6e.

August 1–6: International Congress of Biochemistry, Brussels, Belgium. Professor C. Liebecq, 17 Place Delcour, Liège, Belgium.

August 14–20: Pan American Congress of Rheumatic Diseases, Rio De Janeiro and São Paulo, Brazil. Dr. Waldemaar Bianchi, 126 Avenida Franklin D. Roosevelt, Rio De Janeiro.

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